TROPICAL EOSINOPHILIA
DEMONSTRATION OF MICROFILARIÆ IN LUNG, LIVER, AND LYMPH-NODES

J. K. G. WEBB
M.A., B.M. Oxon., M.R.C.P.
PROFESSOR OF PÆDIATRICS

C. K. JOB
M.D. Madras
LECTURER IN PATHOLOGY

E. W. GAULT
M.D., M.S. Melb., F.R.A.C.S.
PROFESSOR OF PATHOLOGY

CHRISTIAN MEDICAL COLLEGE, VELLORE, SOUTH INDIA

CONSIDERABLE evidence has now accumulated pointing to some form of filarial infection as the cause of tropical eosinophilia (tropical pulmonary eosinophilia, eosinophilic lung) (*Lancet* 1958). It comprises the demonstration of a consistently high titre of filarial complement-fixing antibodies in the serum (Danaraj et al. 1957, 1959), a consistent clinical, hæmatological, and serological response to therapy with the antifilarial, diethylcarbamazine (Danaraj 1958, Ganatra et al. 1958, Baker et al. 1959), and the experimental production of tropical eosinophilia in a volunteer by the subcutaneous injection of infective larvæ of two species of animal filaria (Buckley 1958). The blood is consistently negative for microfilariæ (Danaraj 1958), but microfilariæ have been demonstrated in the lymph-nodes of patients presenting with lymphadenopathy, and massive eosinophilia (Meyers and Kouwenaar 1939, van der Sar and Hartz 1945, Friess et al. 1953). Some of these cases with microfilariæ in lymph-nodes have had respiratory symptoms and radiological evidence of pulmonary infiltration quite consistent with a diagnosis of tropical (pulmonary) eosinophilia. However, microfilariæ have never been identified in the lung lesions of this syndrome.

In 1952 Beaver and his colleagues demonstrated in children in the Southern United States that invasion of internal organs by the larvæ of *Toxocara canis* was the cause of eosinophil granulomata in the liver, pulmonary infiltrations, and a massive eosinophilia in the blood. These workers postulated that a similar mechanism of zoonotic helminthic infection might be responsible for tropical eosinophilia in India. Three years ago a study was initiated by us to try and confirm this hypothesis.

Two years ago, in a preliminary communication (Gault and Webb 1957), we reported the finding of what we then believed to be part of a nematode larva in the liver of a child with tropical eosinophilia. We now report the finding of microfilariæ in lungs, liver, and lymph-nodes of cases satisfying the diagnostic criteria of tropical eosinophilia (Ball 1950, Danaraj 1958) and describe the pathological changes in these tissues. We also describe cases with involvement of lymph-nodes or liver but not lung.

Material and Methods

Clinical Material

For the first four months of 1957, and again since July, 1958, all children seen at the Christian Medical College Hospital, Vellore, who were found to have eosinophilia of more than 4000 per c.mm. have been seen by one of us (J. K. G. W.). From among these children cases have been selected for further study.

In the earlier phase of the investigation concern centred on the question of liver involvement and 5 children with typical pulmonary infiltration and moderate hepatomegaly were selected for open liver biopsy. In addition, liver biopsy has been performed in 1 child with hepatosplenomegaly, but no lung or lymph-node involvement, and in 1 child with lymphadenopathy but no lung involvement.

Throughout the period of the investigation, any opportunity to examine lung tissue has been taken. Tissue has been obtained in this way from a patient admitted under Dr. S. J. Baker, an adult requiring pneumonectomy for a tension cyst of the lung, and from 1 child at the time of ligation of a patent ductus arteriosus. 1 child was admitted specifically for lung biopsy. In addition, one lung resected in 1950 and preserved in formalin was available for pathological studies.

More recently, lymph-node biopsy has been performed in 12 cases—9 with pulmonary infiltrations, and 3 with no evidence of lung involvement.

Clinical Pathology

Absolute eosinophil-counts were done by the method described by Dacie (1956). Blood examinations for microfilariæ included several by the concentration technique described by Knott (1939). The method used for the filarial complement-fixation test (F.C.F.T.) was a modification of that described by Danaraj et al. (1959). Lymph-nodes obtained for biopsy were divided; some of the tissue was processed for histological examination, and some teased in normal saline solution and allowed to stand for several hours at room temperature, the centrifuged deposit then being examined for microfilariæ both in wet preparations and in stained films (Friess et al. 1953).

Histopathology

All tissues were fixed in 10% formalin or Zenker's solution. Complete transverse sections of the two lungs about 0·5 cm. thick were cut, divided into portions of a convenient size, and after processing embedded in paraffin-wax blocks. The lung, liver, and lymph-node biopsy material was divided if necessary and similarly embedded. All of these blocks were sectioned completely at 7 μ. The sections were stained with hæmatoxylin and eosin, and all of each section was searched under the high-power lens (magnification × 450).

Results

LUNG CASES

Case 1.—A man, aged 28, was admitted on Dec. 1, 1950. Three months previously he had developed fever and pain in the chest, followed by persistent cough. He was of poor physique, weighing 88 lb. There was slight impairment of percussion note over the left upper lobe anteriorly, but no adventitious sounds in either lung. Hæmoglobin was 10·75 g. per 100 ml., total leucocytes 22,700 per c.mm. (neutrophils 56%, eosinophils 36%, and lymphocytes 8%) and erythrocyte-sedimentation rate (E.S.R.) 4 and 25 mm. after the first and second hours (Westergren). A chest radiograph showed a dense opacity in the upper zone of the left lung with apparent cavitation. At bronchoscopy the left-upper-lobe bronchi were patent and a bronchogram showed dye entering the lesion. With a provisional diagnosis of lung abscess, left upper lobectomy was performed on Dec. 15. Cough persisted post-operatively, and on Jan. 8, 1951, eosinophils were 63% of a total leucocyte-count of 20,800 per c.mm. This high eosinophilia and the massive eosinophil infiltration found on histological examination of the resected specimen suggested a diagnosis of tropical eosinophilia.

A course of arsenic injections relieved his symptoms completely for eleven months when cough and eosinophilia (white

blood-cells 17,000 per c.mm., eosinophils 53%) were found to have recurred.

Case 2.—A man, aged 22, was admitted on Sept. 11, 1957, with a two-year history of cough and breathlessness. The cough had varied in severity from time to time, had occasionally been accompanied by wheezing and had been productive of up to 10 oz. a day of watery inoffensive sputum which had never been bloodstained. Breathlessness had been severe, ultimately limiting his walking to about one furlong, and present even at rest.

He was a man of poor general physique, weighing 98 lb., dyspnœic at rest though not cyanosed. There was evidence of displacement of the mediastinum to the right, with rhonchi and a few medium crepitations throughout the right lung and at the base of the left lung, and a hyperresonant percussion note with much-diminished breath sounds over the front and most of the back of the left chest. Hæmoglobin was 11·75 g. per 100 ml., total leucocytes 17,500 per c.mm. (neutrophils 26%, eosinophils 62%, and lymphocytes 12%); the E.S.R. was 120 and 130 mm. in the first and second hours (Westergren); the absolute eosinophil-count one week later was 5200 per c.mm. F.C.F.T. was positive at 1 in 40. One blood specimen was negative for microfilariæ. Urine was normal; two stools contained hookworm ova. Two specimens of sputum were negative for tubercle bacilli. Posteroanterior and lateral chest radiographs showed a huge tension cyst occupying most of the left chest, extending across the mediastinum and displacing it to the right; there were also increased reticular markings in the right lung.

On Sept. 19, left pneumonectomy was performed; the post-operative course was uneventful. The patient was then treated with diethylcarbamazine 200 mg. three times daily for one week. After a further week his eosinophil-count was 330 per c.mm and after two weeks 900 per c.mm. and the F.C.F.T. positive at only 1 in 10. At this time he was free from all symptoms.

Case 3.—A boy, aged 11 years, was admitted on Aug. 19, 1959, with a three-month history of cough, occasional wheezing, and breathlessness, all symptoms being worse at night. He was of average physique (weight 43 lb.), cheerful and active. There were rhonchi and medium crepitations throughout both lungs. There was no significant lymphadenopathy; the liver was palpable 1 cm. below the costal margin in the mid-clavicular line and normal in consistence; the spleen was not palpable.

Hæmoglobin was 10·5 g. per 100 ml., total leucocytes 25,000 per c.mm. (neutrophils 30%, eosinophils 44%, basophils 1%, lymphocytes 24%, and monocytes 1%), and absolute eosinophil-count was 9800 per c.mm.; E.S.R. 30 and 69 mm. in the first and second hours (Westergren); F.C.F.T. positive at 1 in 640. Intradermal purified-protein derivative (P.P.D.) was negative with 50 tuberculin units (T.U.). A chest radiograph showed coarse soft mottling throughout both lung fields. In three stools *Entamœba coli* cysts were the only abnormal finding. Six night specimens of blood were negative for microfilariæ, including three by the Knott (1939) concentration technique after prednisolone, 40 mg. daily, had been given for three days.

On Aug. 24 lung biopsy was performed, and on Sept. 1 a five-day course of diethylcarbamazine 100 mg. b.d. was started. He was free of cough by Sept. 6, but rhonchi were still present in the lungs three days later when the eosinophil-count was 2880 per c.mm. On Sept. 16, his lungs were clear, eosinophils 1540 per c.mm. and F.C.F.T. positive at 1 in 160; and on Nov. 13 he was still symptom-free with clear lungs, eosinophils 1200 per c.mm. and F.C.F.T. 1 in 160.

Case 4.—A boy aged 6 years, was admitted on July 11, 1959, with a history of breathlessness from birth and some deformity of the chest-wall, and cough intermittently for three or four years. He was thin and small for his age (weight 32 lb.) with a prominent precordial bulge. His heart was enlarged with a continuous murmur at the base characteristic of patent ductus arteriosus (P.D.A.). There were medium crepitations in both lungs. There was no significant lymphadenopathy, the liver was not enlarged, but the spleen was palpable $2^1/_2$ in. below the costal margin.

Hæmoglobin was 13·25 g. per 100 ml.; total leucocytes 46,000 per c.mm. (neutrophils 4%, eosinophils 77%, and lymphocytes 19%); E.S.R. 40 and 85 mm. in the first and second hours (Westergren). Five night specimens of blood were negative for microfilariæ by Knott's concentration technique. F.C.F.T. was positive at 1 in >1280. Chest radiograph and fluoroscopy showed enlargement of both ventricles of the heart and of the pulmonary conus, and increased pulmonary vascular markings, with coarse mottling throughout both lung fields.

Cardiac catheterisation confirmed the diagnosis of patent ductus arteriosus; and on Aug. 25, after prednisolone had cleared the lungs of moist sounds, the ductus was ligated, lung tissue being taken at the same time for biopsy. The patient made an uneventful recovery from the operation; and on Sept. 13 a five-day course of diethylcarbamazine, 50 mg. t.i.d., was started. On Oct. 22 he was symptom-free with clear lungs, and eosinophils had fallen to 2100 per c.mm. F.C.F.T. was still positive at 1 in >1280.

Pathology

The lung tissue, before fixation, felt soft and spongy, but nodules were readily palpable. The cut surface showed irregularly scattered whitish nodules 3–5 mm. in diameter, the distance between nodules varying from 1 to 3 cm. In one segment of one lung (case 1) there was a larger area of consolidation in which the nodules were closer together.

Microscopic examination of these lungs showed that the architecture was well preserved. There was slight œdema of alveolar walls in most areas. In the vicinity of the nodules there was infiltration of the alveolar walls by eosinophils; and septal cells were protruding into many of the alveoli, some of which contained collections of macrophages.

Nodules were scattered irregularly through the lung, without any particular relation to bronchi or blood-vessels. Some nodules were formed by areas of consolidation involving 20–30 alveoli which were distended with eosinophils enmeshed in fibrin. In the centre of some of these nodules, alveolar walls were destroyed with the formation of an eosinophil abscess (fig. 1), and in the centre of some of these abscesses portions of microfilariæ were found (fig. 3).

In other nodules the central collection of eosinophils was replaced by epithelioid cells, which were sometimes arranged like a palisade round deeply acidophilic hyaline

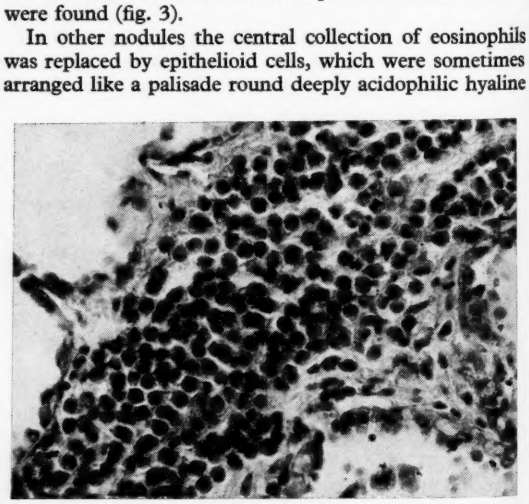


Fig. 1—Lung section showing area of eosinophil aggregates. (H. & E. ×400.)

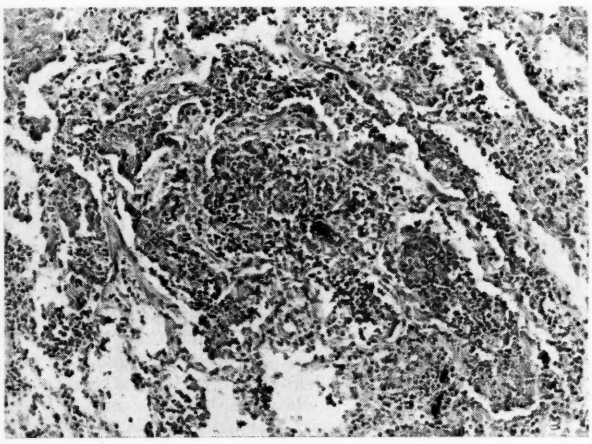


Fig. 2—Lung section showing nodule with granuloma at the centre composed of epithelioid cells surrounding an M.K. body, and surrounding tissue infiltrated with many eosinophils. (H. & E. ×90.)

material (fig. 2). In some instances this hyaline material contained fragments of degenerating larvæ.

Other nodules showed some fibrosis at the periphery. In these, eosinophils were less evident; and at the centre there were epithelioid and giant cells surrounding amorphous hyaline material (figs. 4 and 5). In such nodules no fragments of parasite could be identified.

Parasites

In some 5000 sections examined, five almost complete microfilariæ were found—one in case 1, three in case 2, and one in case 3. Slides containing two of these microfilariæ were sent to Prof. P. C. Beaver (professor of parasitology, University of Tulane, New Orleans, La, U.S.A.), who reported on one which ran through three sections as follows:

"The objects on the slides are indeed portions of a microfilaria. They are serial sections and the three together contain almost all the microfilaria. It is almost certain that only one section is lacking and it contained a small portion of the anterior end and a short segment in the third quarter of the body. The reconstructed portions constitute a length between 200 and 230 microns and the greatest width is approximately 7 microns. There appears to be no question about it having been dead for a brief period before it was fixed."

The other microfilariæ were essentially similar in appearance.

In addition, recognisable fragments of microfilariæ were found in seventeen different nodules. Some of these fragments were found in eosinophil aggregates. Others were in the centre of acidophilic hyaline material, their appearance being suggestive of that described by Meyers and Kouwenaar (1939) and sometimes referred to as Meyers-Kouwenaar (M.K.) bodies.

LIVER CASES

Case 5.—A girl, aged 4½ years, was admitted on Aug. 18, 1958. Her early development had been normal; there was no previous history of significant illness. In the month before admission her parents had noticed her wheezing during sleep, and for three weeks she had been coughing. Her appetite had been poor, but there had been no fever and no obvious reduction of activity.

She was a small undernourished child, weighing 25½ lb. Xerophthalmia was present. There were rhonchi and medium crepitations throughout both lungs. The liver was palpable 2·5 cm. below the costal margin in the midclavicular line, was painless, and felt normal in consistence. The spleen was not palpable. There was no significant lymphadenopathy. Her hæmoglobin was 12·9 g. per 100 ml.; total leucocyte-count 28,200 per c.mm. (neutrophils 18%, eosinophils 65%, and lymphocytes 17%); the E.S.R. was 17 and 31 mm. in the first and second hours. No malarial parasites were seen in a blood-film, and one night specimen of blood was negative for microfilariæ. Urine was normal, and two stools were negative for cysts and ova. An intradermal tuberculin test with 5 T.U. of P.P.D. was negative. F.C.F.T. was positive at 1 in 160. A chest radiograph showed extensive soft miliary mottling throughout both lung fields (fig. 9*a*).

At laparotomy on Aug. 27, the liver was slightly enlarged and normal in general appearance and consistence, but scattered over the anterosuperior surface were 20–30 whitish spots varying from 1–3 mm. in diameter. A piece of tissue including some of these spots was taken for biopsy from the anterior aspect of the left lobe. Recovery from operation was uneventful. The patient was referred to a special clinic for inclusion in a controlled therapeutic trial, but she failed to attend. Contact with her was lost for one year.

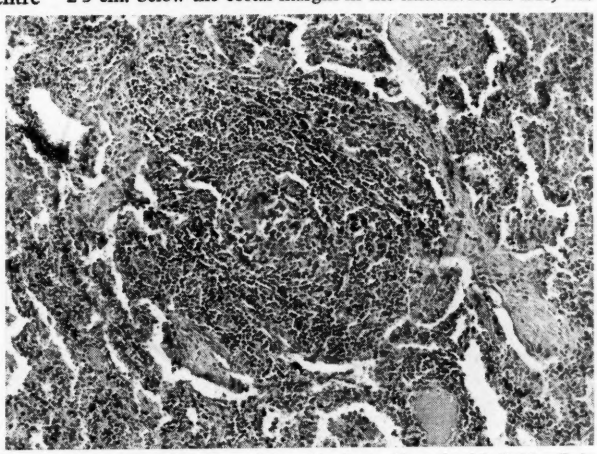


Fig. 4—Lung section showing nodule with giant cells and epithelioid cells in middle surrounded by eosinophils. (H. & E. ×90.)

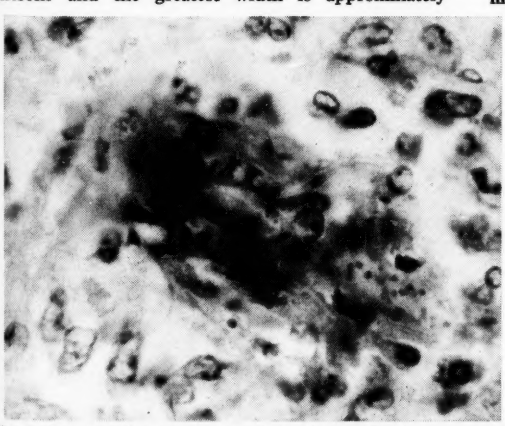


Fig. 3—Lung section showing portion of microfilaria surrounded by eosinophilic material, collections of epithelioid cells at periphery, and fine black dots in body of microfilaria. (H. & E. ×1000.)

SUMMARY OF CLINICAL AND PATHOLOGICAL FEATURES OF CASES

Case no.	Sex	Age (yr.)	Presenting symptoms	Lymph-adenopathy	Hepato-megaly	Lung signs	X-ray evidence of pulmonary infiltration	Typical pathological lesions demonstrated in:	Evidence of microfilariæ in:	F.C.F.T. (dilution)	Thera-peutic response
1	M	28	Cough	0	0	+	+	Lung	Lung	..	+
2	M	22	Cough and breathlessness	0	0	+	+	Lung	Lung	40	+
3	M	11	Cough, wheeze, and breathlessness	0	?+	+	+	Lung	Lung	640	+
4	M	6	Cough and breathlessness (partly due to P.D.A.)	0	0	+	+	Lung	M.K. bodies in lung	>1280	+
5	F	4½	Cough and wheeze ..	0	+	+	+	Liver	Liver	160	+
6	M	7	Anorexia and vague ill health	0	+	0	0	Liver	0	640	+
7	M	7	Cough and wheezing ..	+	0	+	+	Lymph-node	Lymph-node	320	+
8	F	2½	Enlarged lymph-nodes ..	+	+	0	0	Lymph-node	Lymph-node	80	+
9	M	7	Enlarged lymph-nodes ..	+	+	0	0	Liver and lymph-node	Lymph-node	20	?
10	M	6	Cough	+	+	+	+	Lymph-node	Lymph-node	2560	+

On Sept. 1, 1959, she was seen again. Symptoms had subsided gradually after the laparotomy, and she had been regarded by her parents as healthy for the previous nine months. Her lungs were clear, and her liver was no longer enlarged. An absolute eosinophil-count was 2820 per c.mm., and F.C.F.T. still positive at 1 in 160. A chest radiograph showed that the mottling had cleared, but there were still increased linear striations in both lungs. She was treated with diethylcarbamazine 50 mg. three times daily. On Nov. 18 she was symptom-free and had gained weight: the chest radiograph showed further clearing (fig. 9b), eosinophils were 1370 per c.mm., and the F.C.F.T. was positive at 1 in 80.

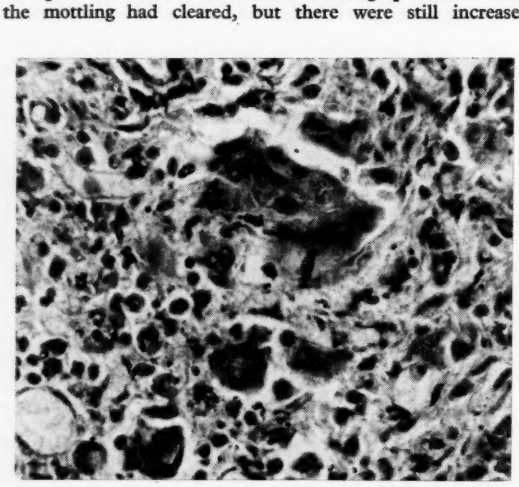


Fig. 5—Centre of nodule in fig. 4 showing eosinophilic hyaline material at centre surrounded by many giant cells, epithelioid cells, and occasional eosinophils. (H. & E. ×520.)

Case 6.—A boy, aged 7 years, was admitted on Aug. 10, 1959, with a rather vague history of ill health for the previous year. Symptoms included anorexia, occasional epistaxis, bouts of fever and cough, and some weight loss. He was a cheerful child, not ill-looking, and of average physique (weight 42 lb.). There was no significant lymphadenopathy, the lungs were clear, the liver was enlarged 3·5 cm. below the costal margin in the midclavicular line and 5·0 cm. in the midline, and slightly firmer than normal in consistence, and the spleen was palpable 5 cm. below the costal margin.

Hæmoglobin was 10·0 g. per 100 ml.; total leucocytes 38,500 per c.mm. (neutrophils 10%, eosinophils 77%, and lymphocytes 13%); total eosinophils 28,645 per c.mm. Four night specimens of blood were negative for microfilariæ. F.C.F.T. was positive at 1 in 640. Total serum-protein was 8·2 g. per 100 ml., icteric index 4 units, thymol turbidity 2 units, thymol flocculation ++, and zinc-sulphate turbidity 6 units. Platelets were 310,000 per c.mm.; and bleeding, clotting, and prothrombin times normal. The bone-marrow was normoblastic, with no abnormality apart from the eosinophilia. A chest radiograph showed faint reticular markings in both lungs of very doubtful significance; a barium swallow showed no evidence of œsophageal varices.

At laparotomy on Aug. 24, the liver was considerably enlarged and densely studded with white spots about 2 mm. in diameter; the spleen was enlarged to about three times the normal size, felt firm in consistence, and showed a pronounced perisplenitis. Tissue was taken from the liver for biopsy, but none from the spleen. On Sept. 1 a five-day course of diethylcarbamazine 100 mg. b.d. was started. On Nov. 4 the liver was palpable 2·5 cm. below the costal margin, and the eosinophils were 12,130 per c.mm. A second five-day course of diethylcarbamazine, 200 mg. b.d., was given. On Nov. 14 the liver had receded further to 1·5 cm. in the midclavicular line, and the eosinophils were 4200 per c.mm. On Nov. 25 the eosinophils had dropped to 1570 per c.mm. and the F.C.F.T. was positive at 1 in 640.

Pathology

In addition to these two cases (5 and 6) and case 9, reported below, liver tissue was obtained by open biopsy from a further four children, with typical tropical (pulmonary) eosinophilia. In these seven children the surface of the liver was found at laparotomy to be studded with whitish dots 2–5 mm. in diameter. In some there were

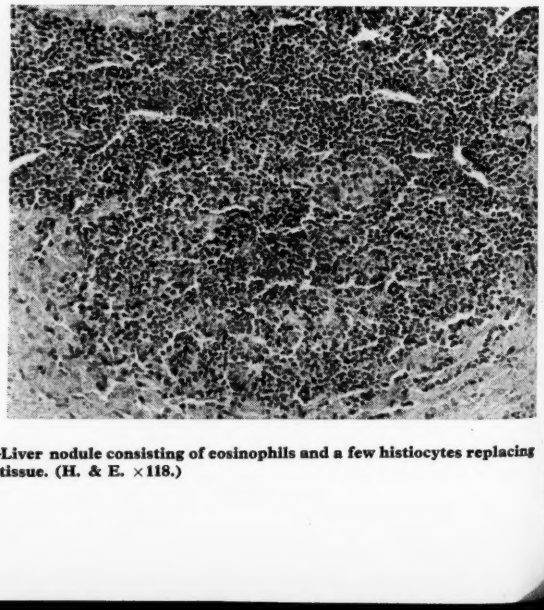


Fig. 6—Liver nodule consisting of eosinophils and a few histiocytes replacing liver tissue. (H. & E. ×118.)

only 4–5 of these dots, in others 20–30, and in one (case 6) there were hundreds.

On microscopic examination the normal lobular pattern of the liver was preserved. The cells were well glycogenated, and there was no evidence of fatty change or congestion. There was patchy infiltration by eosinophils round portal tracts; in some instances this infiltration was slight, in others very extensive. In addition nodules were scattered through the liver parenchyma in each of the seven livers examined. These nodules bore no constant relation to the lobular pattern. The structure of these nodules was essentially similar to that of those seen in the lungs, varying from lakes of eosinophils to mature granulomata containing giant and epithelioid cells (figs. 6 and 8).

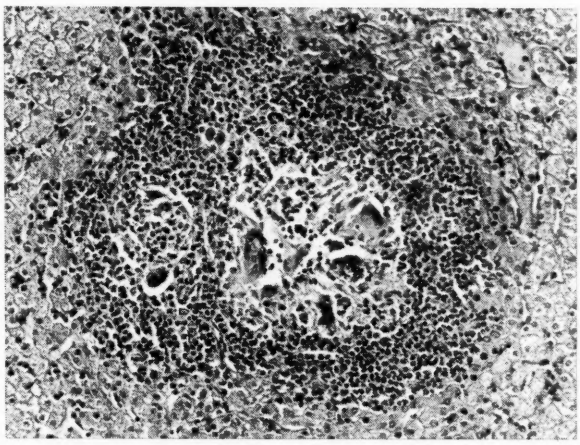


Fig. 8—Liver showing granuloma consisting of giant cells in middle surrounded by epithelioid cells and many eosinophils. (H. & E. ×130.)

Parasites

In some 3000 sections examined, one almost complete microfilaria was found in the centre of an aggregate of eosinophils (case 5). The organism ran, in all, through nine serial sections. In seven of the sections the cuts through the parasite were either transverse or only slightly oblique. These sections included a portion of the microfilaria measuring 60–70 μ in length. In three of these transverse sections the organism was encased in a collar of acidophilic hyaline material. In the eighth section a curved and thinned-out portion approximately 20 μ in length could be seen and, separated from this by a distance of 40 μ, another piece of the organism 10 μ in length which was probably one end. The ninth section included the greatest length of the organism—about 85 μ (fig. 7). The total length included in these sections was at least 160 μ, the greatest width 6–7 μ. Although in some portions the details were indistinct, in others the outline of the body and the contained nuclei were readily apparent.

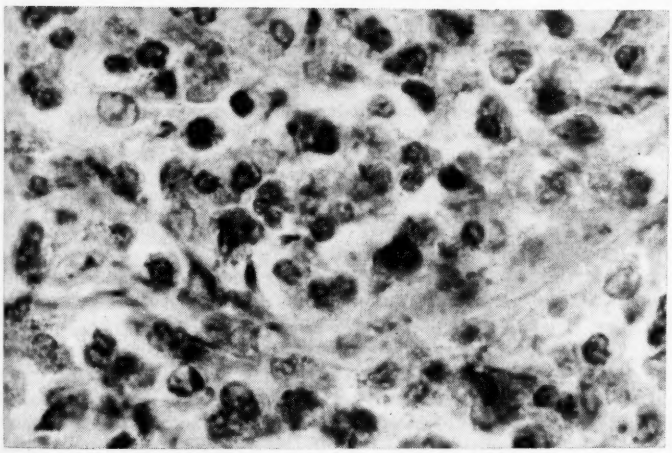


Fig. 7—Liver showing microfilaria in middle of eosinophilic aggregate, and the long larva with dots in its body crossing the field. (H. & E. ×1000.)

These sections have been seen by Professor Beaver, who confirmed that the organism was a microfilaria.

In two other livers, lesions suggestive of M.K. bodies were seen, but no recognisable portions of parasite were found.

LYMPH-NODE CASES

Case 7.—A boy, aged 7 years, was admitted on Aug. 29, 1959, with a six-month history of cough and wheezing. Cough had first developed during a five-day febrile illness, but persisted after subsidence of the fever: both cough and the tendency to wheeze had been worse at night. His general nutrition was fair (weight 40 lb.). There were rhonchi throughout both lungs. The liver was just palpable at the costal margin; the spleen could not be felt. The axillary and inguinal lymph-nodes were moderately enlarged, the largest being in the left axilla and measuring 2·0 cm. in diameter: they were firm, mobile, and painless.

Hæmoglobin was 11·9 g. per 100 ml.; total leucocytes 29,400 per c.mm. (neutrophils 16%, eosinophils 59%, and lymphocytes 25%); absolute eosinophil-count 17,200 per c.mm. Six night specimens of blood were negative for microfilariæ, including three by the Knott concentration technique. F.C.F.T. was positive at 1 in 320. Intradermal P.P.D. was negative with 5 T.U. A chest radiograph showed dense mottling and strikingly increased reticular markings throughout both lung fields (fig. 10*a*).

On Sept. 3 the largest node in the left axilla was removed for biopsy, and on Sept. 10 a five-day course of diethylcarbamazine, 100 mg. b.d., was started. Symptoms were

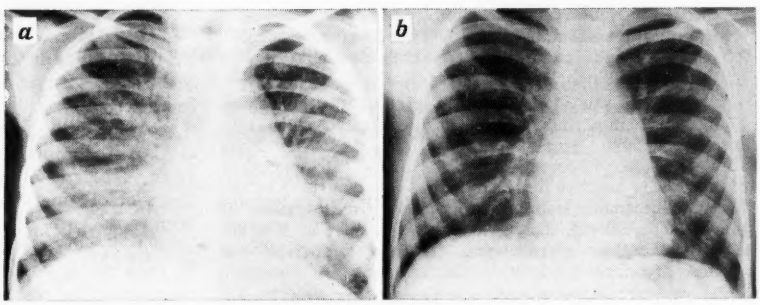


Fig. 9—Chest radiographs of case 5: *a*, before treatment; *b*, after treatment.

Fig. 10—Chest radiographs of case 7: *a*, before treatment; *b*, after treatment.

relieved almost immediately, and the absolute eosinophil-count was 5300 per c.mm. on Sept. 20 and 1706 per c.mm. on Sept. 29. On Nov. 3 the patient was symptom-free, the eosinophil-count was 1980 per c.mm., and the F.C.F.T. was positive at 1 in 320. On Nov. 25 he was still symptom-free, eosinophils were 1560 per c.mm., and the F.C.F.T. titre had fallen to 1 in 80.

Case 8.—A girl, aged 2½ years, was seen on April 14, 1959. Her father, who was a doctor, had found two days previously a moderate generalised enlargement of lymph-nodes, but apart from this finding she had no symptoms. She was a small active child (weight 23 lb.). Lymph-nodes in all groups were slightly enlarged, mobile, and painless: the largest were in the right axilla and measured 2·5 cm. in diameter. The lungs were clear. The liver was palpable 4 cm. below the costal margin in the midclavicular line and 5 cm. in the midline, and felt slightly firmer than normal in consistence; the spleen was palpable 2 cm. below the costal margin.

Hæmoglobin was 8·0 g. per 100 ml., and total leucocytes were 22,000 per c.mm. (neutrophils 26%, eosinophils 50%, lymphocytes 20%, and monocytes 4%); an absolute eosinophil-count 14,000 per c.mm. Three night specimens of blood were negative for microfilariæ by the Knott concentration technique—one after twenty-four hours of prednisolone. F.C.F.T. was positive at 1 in 80. A chest radiograph was normal.

Lymph-node biopsy was performed on April 15, and on April 19 a five-day course of diethylcarbamazine, 125 mg. daily, was started. On April 27 an absolute eosinophil-count was 5300 per c.mm. The patient was then not seen again until Aug. 11 when the hepatosplenomegaly had subsided, an eosinophil-count was 940 per c.mm., and the F.C.F.T. was positive at 1 in 10.

Case 9.—A boy, aged 7 years, was admitted on April 20, 1959, on account of a swelling which had been present in the right axilla for three months. During this period he had had two brief episodes of fever, cough, and wheezing, but apart from these had remained well. He was of fair general nutrition and physique, weighing 32 lb. There was generalised modest lymphadenopathy, nodes measuring 1–1·5 cm. in diameter, except in the right axilla where one was 3·0 cm.; all nodes were firm, mobile, and painless. The liver was palpable 2·5 cm. below the costal margin in both the midclavicular line and the midline. The lungs were clear.

Hæmoglobin was 11·5 g. per 100 ml. and total leucocytes 17,100 per c.mm. (neutrophils 25%, metamyelocytes 1%, eosinophils 59%, lymphocytes 13%, and monocytes 2%); absolute eosinophil-count 9200 per c.mm. Ten specimens of blood were negative for microfilariæ—seven of these by the Knott concentration technique, four after a five-day course of prednisolone, 30 mg. daily. F.C.F.T. was positive at 1 in 20. A stool contained giardia cysts. A chest radiograph was normal.

On April 22 a lymph-node was removed, and on May 2 laparotomy was performed. The liver was slightly enlarged with white dots scattered over the surface; tissue was taken for biopsy. On May 12 a five-day course of diethylcarbamazine, 50 mg. t.i.d., was started. Unfortunately, contact with this child was then lost.

Case 10.—A boy, aged 6 years, was admitted on May 4, 1959, with a two-year history of cough, productive during the previous month, and occasional fever and wheezing. He was of average physique and nutrition (weight 36½ lb.). There was a group of enlarged lymph-nodes in the right axilla; these were firm, mobile, and painless, the largest measuring 2·5 × 3·5 cm. Nodes in other groups were palpable but not significantly enlarged. The lungs were clear; the liver was palpable 2 cm. below the costal margin in the midclavicular line, and normal in consistence; the spleen was palpable 1·5 cm. below the costal margin.

Hæmoglobin was 10·25 g. per 100 ml.; total leucocytes 27,000 per c.mm. (neutrophils 17%, eosinophils 68%, and lymphocytes 15%); absolute eosinophil-count 14,650 per c.mm. Eight night specimens of blood and 1 day specimen of blood were negative for microfilariæ by the Knott concentration technique—four of them after a four-day course of prednisolone, 40 mg. daily. F.C.F.T. was positive at 1 in 2560. A chest radiograph showed coarse reticular markings in the upper zone of the right lung suggestive of cystic bronchiectasis but no diffuse changes characteristic of tropical eosinophilia. A stool was negative for cysts and ova.

On May 9 lymph-node biopsy was performed. On recovery the patient was taken home unexpectedly before receiving diethylcarbamazine. He was seen again on June 12, when he was symptom-free with an eosinophil-count of 16,400 per c.mm. He returned on Aug. 21, moderately ill, with productive cough and fever and signs suggesting pneumonia in the bronchiectatic right lung. This responded to penicillin and sulphadimidine. On Aug. 26, although no specific therapy had been given, an absolute eosinophil-count was 40 per c.mm.; the F.C.F.T. was still positive at 1 in 640. He was not seen again until Nov. 13, when he still had cough and scattered rhonchi in both lungs with eosinophils 4200 per c.mm. and F.C.F.T. positive at 1 in 2560. He was treated with diethylcarbamazine 100 mg. b.d. for five days. On Dec. 2 he was remarkably improved with no cough, clear lungs, and eosinophils 2400 per c.mm. (The low eosinophil-count on Aug. 25 was probably due to the stress of an intercurrent infection. We have observed similar falls in eosinophil-counts after surgical operations.)

Pathology

The lymph-nodes from these four cases were soft and fleshy in consistence. Their greatest diameters varied from 2·0 to 3·5 mm. The cut surfaces showed circumscribed areas, brownish or greyish-white and about 1 mm. in diameter, scattered irregularly through the node.

The miscroscopic appearances were similar in each of the nodes. The architecture was largely preserved. Germinal follicles were prominent, and there was a diffuse increase of vascularity with endothelial proliferation. The most striking abnormality was in the medullary cords and lymph sinuses, where there were numerous large aggregates of eosinophils. These aggregates varied considerably in size. They were much less frequently seen in the cortex, though a few were present in the subcapsular region. In the centre of some of these aggregates in each node, portions of microfilariæ were seen. The capsules of the nodes were thickened and infiltrated with many eosinophils and lymphocytes.

Parasites

Wet-drop preparations of the centrifuged deposits of nodes teased in saline were positive for live microfilariæ in cases 7, 8, and 10. In stained films the microfilariæ were sheathed, measured about 300 μ in length, and in each case showed the anatomical features characteristic of *Wuchereria bancrofti*. Stained films from case 8 were sent to Professor Beaver, who reported that he found no reason for not calling these *W. bancrofti*.

In each of the four cases, portions of microfilariæ were found in the centre of some of the eosinophil aggregates. In some instances they could be traced through serial sections as complete or almost complete organisms.

Discussion

Evidence of Filarial Infection

To the evidence of filarial infection as a cause of tropical eosinophilia previously provided by serology, therapeutic response, and experimental infection of a volunteer, we have now added the demonstration of microfilariæ in the lung. The fact that the organisms found were always in the centre of an intense eosinophil or granulomatous reaction leaves no room for doubt about their causal role. Although it is reasonable to assume that all the lung lesions are a reaction to invading microfilariæ, it is important to recognise that almost complete microfilariæ, confidently identifiable as such, were found in only two of the four lungs studied (cases 2 and 3). However, portions of microfilariæ were clearly recognisable in case 1, and case 4 showed typical M.K. bodies. These positive findings need to be viewed against the negative evidence of previous reports on the pathology of the lung in tropical eosinophilia.

Viswanathan (1948) found no tissue parasites in the lung he studied, but he made no special search of serial sections, and without this the chances of finding a parasite are extremely slender. Our experience is that these organisms are found only after detailed search under the high power of all the serial sections through a large number of lesions. Danaraj (1959), on the other hand, did make a detailed search for tissue parasites; but his patient had died from arsenical encephalopathy eight days after starting a course of arsenic, and it seems possible that in this case the arsenic had already killed any organisms present, which had subsequently degenerated beyond recognition.

The demonstration of microfilariæ in liver lesions indicates that filarial infection is a possible cause of hepatomegaly with eosinophilia. This is a new finding. The demonstration of microfilariæ in lymph-nodes confirms that this syndrome of lymphadenopathy with eosinophilia due to some form of filarial infection, previously described in patients from the West Indies (van der Sar and Hartz 1945), Indonesia (Meyers and Kouwenaar 1939), and North Vietnam (Friess et al. 1953), also occurs in India. The implications of these findings, and their relation to tropical eosinophilia will be discussed in the next section.

Clinical Profiles

Tropical eosinophilia most commonly presents as a respiratory disease. In fact, the diagnosis will rarely be considered unless respiratory symptoms and clinical and radiological evidence of pulmonary infiltration are present.

In a careful study of 123 cases in Malaya, Danaraj (1959) states that hepatosplenomegaly and generalised lymphadenopathy were not evident. On the other hand, Ball (1950), working at Vellore, found significant lymphadenopathy in 57 and moderate hepatomegaly in 27 of 100 cases. Similarly Baker et al. (1959) found enlarged lymph-nodes in 16·5% and slight to moderate enlargement of the liver in 24% of 165 cases, the spleen being palpable in a third of the patients with enlarged livers. They noted that in all cases the lymphadenopathy subsided with successful treatment. The absence of hepatic and lymph-node involvement in the Malayan cases and the relatively high incidence observed at Vellore can be partly explained by age difference. Only 3·6% of Danaraj's cases were under 10 years of age, compared with 43% of Baker's series. Ball found a higher incidence of hepatomegaly and lymphadenopathy in children than in adults—45% compared with 16%, and 76% compared with 24%, respectively.

The demonstration of eosinophil aggregates or granulomata in all the livers and in one of the lymph-nodes, together with microfilariæ in two instances, in typical cases of tropical (pulmonary) eosinophilia indicates that both liver and lymph-nodes may be involved in this disease. Liver involvement has not hitherto been proved, but lymph-node involvement has been suggested by previous workers. One at least (case 1) of the cases reported by van der Sar and Hartz (1945) possibly one (case 2) of those reported by Meyers and Kouwenaar (1939), and several of those reported by Friess et al. (1953) certainly had sufficient respiratory symptoms and signs to qualify for the diagnosis of tropical (pulmonary) eosinophilia. Nevertheless, there has been a tendency in the past, especially in India, to regard cases with significant lymphadenopathy as atypical, and therefore perhaps distinct ætiologically from the common respiratory form of the disease. In our opinion this view is no longer tenable. One of our cases in which a microfilaria was found in the liver (case 5) and one of those with microfilariæ in the lymph-node (case 7) presented with respiratory symptoms and signs dominating the clinical picture, and both had dense mottling in chest radiographs indicating extensive pulmonary infiltration (figs. 9 and 10). These cases are absolutely typical of tropical (pulmonary) eosinophilia; the hepatomegaly and lymphadenopathy were relatively inconspicuous and their true significance was only revealed by biopsy.

Our cases 6, 8, 9, and 10, would not normally be regarded as examples of tropical eosinophilia, in that they showed no evidence of lung involvement. They are distinguishable, however, only on this basis. The massive eosinophilia, the histopathological lesions, the presence of microfilariæ in all except one (case 6), the positive F.C.F.T., and the response to diethylcarbamazine are all identical with the lung cases. Moreover, the lung cases included examples of lesions apparently confined to the lung, of lesions of lung and liver combined, and of lung and lymph-node lesions combined. Among the cases with no lung involvement were examples of isolated lymphadenopathy, of combined lymph-node and liver involvement, and of isolated liver lesions possibly combined with splenic lesions but certainly without lung or lymph-node involvement. To separate these cases into distinct disease entities appears to us unreasonable.

All the cases reported here have a common ætiology—namely, infection with some form of filaria. Possibly different filariæ are involved, and particular clinical profiles are associated with different species. Until this has been proved, however, it seems reasonable to enlarge the concept of tropical eosinophilia to embrace the non-pulmonary forms of the disease, and to use the descriptive qualifications pulmonary, hepatic, and lymphatic when necessary. On the other hand it seems desirable to reserve the diagnosis of tropical eosinophilia for those cases where a filarial infection is suspected or proved. Similar syn-

dromes are certainly caused by other parasites—e.g., *Toxocara canis* (Beaver et al 1952, Chaudhuri and Saha 1959)—but probably the F.C.F.T. will serve to differentiate these.

Pathogenesis

It now seems clear that tropical eosinophilia in all its possible clinical manifestations is usually due to infection with some form of filaria. The demonstration of microfilariæ in lesions in lung, liver, and lymph-nodes implies at least two things. First, infective larvæ introduced by mosquito-bite must have developed somewhere in the body into sexually mature adult filariæ capable of producing microfilariæ. The intervals of fourteen and ten weeks in Buckley's (1958) experiments between the injection of infective larvæ and the development of cough and eosinophilia is consistent with this idea (Edeson and Wharton 1957). Secondly, the lesions in all the tissues involved in tropical eosinophilia appear more likely to be due to direct invasion by microfilariæ than to be the result of visceral allergy provoked by some remotely situated organism.

It seems reasonable to suppose that during the active phase of the disease microfilariæ continue to be liberated from the adult worms only to become trapped in the tissues, dying there and exciting the characteristic eosinophilic reaction. Fragments of disintegrating microfilariæ must continue to excite a vigorous reaction long after the disappearance of anything recognisable histologically as part of an organism. This would partly explain the relatively small proportion of nodules which are found to contain organisms. The duration of symptoms must depend on the survival-time of the adult filariæ, though reinfection is clearly possible at any time. It seems difficult to explain the wide dissemination of lesions in tropical eosinophilia except on the basis of hæmatogenous spread of the microfilariæ. This must be reconciled with the consistent absence of microfilaræmia, even after prednisolone. The explanation may be that the microfilariæ after release into the blood-stream are trapped in the first set of capillaries through which they pass. This will normally be in the lung, which would account for the predominance of pulmonary involvement in this disease. The alternative hypothesis that dissemination is confined to the lymphatic system is difficult to accept.

The particular tissue response to microfilariæ characteristic of tropical eosinophilia is almost certainly related to the species of filaria involved. Buckley's (1958) experiments have provided the strongest possible evidence that this filaria is of animal origin. Unfortunately, in none of the cases reported in this paper has a specifically identifiable microfilaria been found in viscera. It is reasonable, however, to assume that in case 7 similar microfilariæ to those found in the lymph-node were responsible for the lung lesions. These microfilariæ are morphologically indistinguishable from those of *W. bancroftil*. This finding does not, however, rule out the possibility that they are of animal origin. Edeson et al. (1955) reported the recovery of sheathed microfilariæ indistinguishable from *W. malayi* from five different species of animal in Malaya. Further observations on the life-cycles of these microfilariæ revealed that at least two species of filaria were involved. On the strength of this evidence Buckley (1958) has pointed out that the identification as *W. malayi* of microfilariæ found in gland biopsies by the Dutch and French workers is open to doubt. Similarly, the microfilariæ found in the cases reported here may be bancroftitype microfilariæ of animal origin, but this at the moment is speculation.

Summary

The pathological changes in the lung, liver, and lymph-nodes of typical cases of tropical pulmonary eosinophilia are described.

Microfilariæ have been demonstrated in the centre of nodules in each of these tissues, suggesting that direct invasion by these organisms is the cause of the lesion in this disease.

Cases are reported with lymph-node and hepatic, but without lung, involvement. The lesions in these cases were similar to those seen in the lung, and microfilariæ were present. A plea is made to enlarge the concept of tropical eosinophilia to include such cases, and at the same time to restrict the diagnosis to those in which a filarial infection is proved or suspected.

Microfilariæ recovered from lymph-nodes have been provisionally identified as *W. bancrofti*-type; but, on the analogy of findings in Malaya, these may be of animal origin, and zoonotic filariasis remains the most likely explanation of tropical eosinophilia.

It is a pleasure to acknowledge the many ways in which Prof. P. C. Beaver has helped and encouraged us; in particular we are grateful to him for the photomicrographs of the lung and liver sections, and for the supplies of *Dirofilaria immitis* antigen used in the F.C.F.T. We are grateful to many colleagues, both surgical and medical—particularly to Dr. R. H. Betts, head of the thoracic unit, who performed all the thoracotomies, to Dr. S. J. Baker, associate professor of medicine, for case 2, to Dr. Ruth M. Myers, professor of microbiology for carrying out the F.C.F.TS., and to junior colleagues in the pædiatric department for their recognition and care of many of the cases. We are also most grateful to Messrs. Burroughs, Wellcome for a grant which covered some aspects of this study.

REFERENCES

Baker, S. J., Rajan, K. T., Davadatta, S. (1959) *Lancet*, ii, 144.
Ball, J. D. (1950) *Trans. R. Soc. trop. Med. Hyg.* **44**, 237.
Beaver, P. C., Snyder, C. H., Carrera, G. M., Dent, J. H., Lafferty, J. W. (1952) *Pediatrics*, **9**, 7.
Buckley, J. J. C. (1958) *Trans. R. Soc. trop. Med. Hyg.* **52**, 335; *E. Afr. med. J.* **35**, 493.
Chaudhuri, R. N., Saha, T. K. (1959) *Lancet*, ii, 493.
Dacie, V. (1956) Practical Hæmatology. London.
Danaraj, T. J. (1958) *Quart. J. Med.* **27**, 243.
— (1959) *A.M.A. Arch. Path.* **67**, 515.
— da Silva, L. S., Schacher, J. F. (1957) *Proc. Alumni Ass. Malaya*, **10**, 109.
— — — (1959) *Amer. J. trop. Med. Hyg.* **8**, 151.
Edeson, J. F. B., Wharton, R. H. (1957) *Trans. R. Soc. trop. Med. Hyg.* **51**, 366.
— — Buckley, J. J. C. (1955) *ibid.* **49**, 604.
Friess, J., Pierrou, M., Segalen, J. (1953) *Bull. Soc. Path. exot.* **46**, 1037.
Ganatra, R. D., Sheth, U. K., Lewis, R. A. (1958) *Indian J. med. Res.* **46**, 205.
Gault, E. W., Webb, J. K. G. (1957) *Lancet*, ii, 471.
Knott, J. (1939) *Trans. R. Soc. trop. Med. Hyg.* **33**, 191.
Lancet (1958) ii, 84, 737.
Meyers, F. M., Kouwenaar, W. (1939) *Geneesk. Tijdschr. Ned-Ind.* **79**, 853.
van der Sar, A., Hartz, P. H. (1945) *Amer. J. trop. Med.* **25**, 83.
Viswanathan, R. (1948) *Quart. J. Med.* **17**, 257.

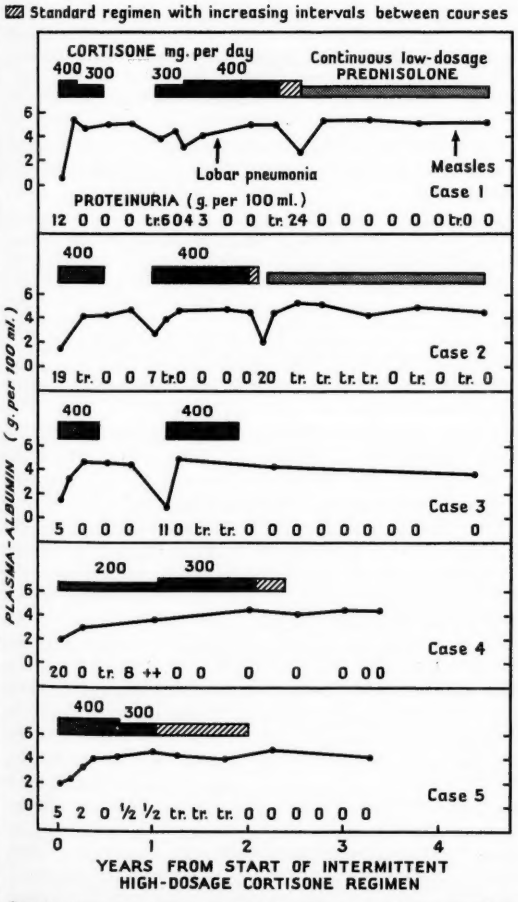
"... Suppose that a conspiracy of unusually public-spirited scientists were to study all the accidental deaths in the world, famine, traffic, and disease included, and by an effort of international cooperation could fabricate evidence that these accidents were really the work of a malicious adversary—say the Martians; the devil is too long dead. Suppose they successfully kidded and frightened their governments—exactly as they have to do now when a constructive proposal needs to be got through. They would find that the protein deficiencies in Africa were part of an organised strategy of conquest; and protein deficiency would be gone in one year, not ten."—Dr. ALEX COMFORT, *Listener*, March 24, 1960, p. 547.

THE NEPHROTIC SYNDROME
TREATED WITH CORTISONE IN INTERMITTENT HIGH DOSAGE

R. G. MITCHELL
M.D. Edin., F.R.C.P.E., D.C.H.

PÆDIATRICIAN, DUNDEE ROYAL INFIRMARY;
LECTURER, DEPARTMENT OF CHILD HEALTH, UNIVERSITY OF ST. ANDREWS

ALTHOUGH steroid therapy represents a great advance in the symptomatic treatment of the nephrotic syndrome in childhood, its influence on the outcome of the disease is still uncertain (Burke 1958, Kohn 1958). In 1951, Lange and his colleagues in New York introduced a regimen involving very large doses of cortisone given intermittently over long periods, and cited experimental evidence that such a scheme might inhibit the nephrotic process long enough to effect a permanent cure (Lange et al. 1953, 1955). In the past few years others, in the United States and France, have advocated this type of treatment (Piel and Williams 1957, Debré et al. 1956), but in this country continuous low-dosage therapy has been favoured (Arneil 1958). Recently, however, it has been suggested that intermittent high dosage with steroids might be the treatment of choice (*Lancet* 1958), and an account of its use in a small group of children is therefore of interest.


Standard regimen with increasing intervals between courses
CORTISONE mg. per day
400 300
300 400
Continuous low-dosage PREDNISOLONE
Lobar pneumonia
Measles
Case 1
PROTEINURIA (g. per 100 ml.)
12 0 0 0 tr.6 0 4 3 0 0 tr. 2 4 0 0 0 0 0 0 tr. 0 0
400 400
Case 2
19 tr. 0 0 7 tr. 0 0 0 0 2 0 tr. tr. tr. tr. 0 tr. 0 tr. 0
400 400
Case 3
5 0 0 0 1 1 0 tr. tr. 0 0 0 0 0 0 0 0 0
200 300
Case 4
2 0 0 tr. 8 ++ 0 0 0 0 0 0 0
400 300
Case 5
5 2 0 ½ ½ tr. tr. tr. 0 0 0 0 0 0
PLASMA-ALBUMIN (g. per 100 ml.)
0 1 2 3 4
YEARS FROM START OF INTERMITTENT HIGH-DOSAGE CORTISONE REGIMEN

Steroid therapy, plasma-albumin levels, and urinary protein in five cases of nephrotic syndrome.

Because more than a third of all children with nephrosis recover either spontaneously or after a single course of hormone treatment (Mateer et al. 1957, Vernier et al. 1958), a very large number of previously untreated cases would be required to establish the superiority of a high-dosage steroid regimen over continuous low-dosage therapy. But if one could show that a high-dosage regimen consistently cured nephrosis which had not responded to other treatment schemes, or had remitted and later relapsed, fewer cases might suffice to establish its greater efficacy. Accordingly, in 1955, the Lange treatment was introduced for all children with nephrosis, attending the Dundee Royal Infirmary, who had failed to respond to one or more courses of hormone therapy or who had relapsed after a temporary remission. This report is based on experience with five such children who started the regimen between April, 1955, and July, 1956, and whose progress has been followed for at least 3 years.

The Study

The terms "nephrotic syndrome" and "nephrosis" are here used to indicate a syndrome of unknown ætiology characterised by œdema, proteinuria, hypoalbuminæmia, and hypercholesterolæmia. No attempt has been made to distinguish between lipoid nephrosis and nephrotic nephritis (Arneil 1958). In assessment even a trace of protein in the urine was regarded as a sign that the nephrotic process might still be active.

The Patients

All the children were girls, and all had severe œdema, hypoalbuminæmia and proteinuria when the Lange treatment was begun (see figure). Their ages ranged from $4^1/_2$ to $12^3/_4$ years, and the nephrotic syndrome had lasted from 9 months to 3 years. All the children had had hormone treatment, either unsuccessfully or with subsequent relapse (see table for details).

The Regimen

At the start of the intermittent high-dosage regimen, corticotrophin was given intramuscularly in a dose of 20 mg. twice daily for 14 days. Although this dose is smaller than that recommended by Lange (Lange et al. 1957), it resulted in satisfactory diuresis and disappearance of œdema in all except one child (case 5) whose œdema did not disappear completely until the 2nd week of maintenance therapy.

5 days after the course of corticotrophin was completed, treatment with cortisone acetate was begun; 100 mg. was given by mouth every 6 hours for 3 consecutive days, the total dose thus being 1200 mg. After 4 days without hormone treatment, this 3-day course was repeated. The regimen of 3 days' treatment in each week was then continued until the recommended number of courses had been given. When this treatment was first used in cases 1–3, cortisone was stopped abruptly after 20 weeks, a period chosen because Lange et al. (1955) had reported that shorter periods did not prevent relapses. But in the later treatment of these cases, and in cases 4 and 5, the aim was a minimum of 52 weeks' high-dosage therapy, as advised by Lange et al. in 1957 and 1958, followed by gradual lengthening of the interval between the 3-day courses over several months.

The corticotrophin was given in hospital, and the children usually went home after 2 weeks' cortisone maintenance therapy. Fluid intake was not restricted, and additional potassium was not given except at the time of the initial diuresis. After the acute phase the children were encouraged to eat a diet rich in protein and without added salt, but no attempt was made to control their diets more accurately. From the beginning of treatment, 1 tablet of penicillin G (200,000 units) was given twice daily as a prophylactic, and this is being continued in all except one child (case 3).

DETAILS OF STEROID TREATMENT IN FIVE CASES OF THE NEPHROTIC SYNDROME

Case no.	Age (yr.)		Previous treatment		First intermittent high-dosage regimen		Time between end of first series and clinical relapse	Second intermittent high-dosage regimen		Time between end of first series and clinical relapse	Present age (yr.)
	At onset of nephrotic syndrome	At start of intermittent high-dosage regimen	Steroid	Total no. of days	No. of weekly 3-day courses	Total daily dose of cortisone (mg.)		No. of weekly 3-day courses	Total daily dose of cortisone (mg.)		
1	4¾	5½	Corticotrophin	12	6 } 22 16 }	400 300	6 mos.	16 } 70 54 }	300 400	3 mos.	10
2	8¾	9½	"	14	20	400	6 mos.	52	400	2½ mos.	13¾
3	4½	6¾	Cortisone	15	20	400	8 mos.	36	400	No relapse in 30 mos.	11¼
4	3½	4½	Corticotrophin, cortisone	18 60	52	200	Proteinuria still present	54	300	No relapse in 17 mos.	7¾
5	9¾	12¾	Corticotrophin, cortisone, prednisolone	183 30 22	33 } 54 21 }	400 300	No relapse in 26 mos.	..	..	..	16

Results

The details of treatment and the further progress of each patient are shown in the figure and table.

In case 1 the daily dose of cortisone was reduced from 400 to 300 mg. after six 3-day courses because the blood-pressure rose to 140/100 mm. Hg and remained at that level, falling to 130/95 only after the dose had been reduced. In her second series of courses the daily dose was 300 mg. at first, but it was increased to 400 mg. after sixteen courses because of a slight clinical relapse. The diastolic pressure remained below 100 mm. Hg despite the increase.

The first two patients (cases 1 and 2) were free from signs of nephrosis while on the full maintenance regimen, but in both of them, severe proteinuria and moderate œdema recurred within 3 months of starting to reduce the dosage, although each had had a full year of treatment. In view of the failure to cure the nephrosis, and the high cost of the regimen, these two girls were afterwards maintained continuously on prednisolone in low dosage; both are now well, although occasional slight proteinuria probably indicates that the nephrotic process is still active.

Case 3 relapsed after the first maintenance period of 20 weeks, and during the second period the child left the district. But the full maintenance regimen was continued for 36 weeks, and then it was stopped because her blood-pressure was persistently 140/100 and her weight was increasing. She had been difficult to manage for a while before cortisone was stopped, but this may have been a side-effect of the treatment as her temperament improved afterwards.

Because case 4 was so young, the standard regimen was modified, and cortisone 200 mg. was given daily. After fifty-two 3-day courses, however, she still had some proteinuria, and for the second series of courses the daily dose was increased to 300 mg. without untoward effect. This is the dose recommended by Lange et al. (1958) for children weighing less than 40 lb.; since the child weighed 38 lb. at the time, it represents the full maintenance treatment, which was continued for 54 weeks and followed by gradual withdrawal of cortisone over 24 weeks.

In case 5 the daily dose was reduced from 400 mg. to 300 mg. after 33 weeks because the blood-pressure rose to 160/110. 2 months later it was 150/100, and then it fell to 140/95. Because the urine contained a very faint trace of protein after 54 weeks' maintenance therapy, the dose was reduced by increasing the interval between courses very slowly, cortisone not being finally withdrawn until nearly a year later when all proteinuria had disappeared.

Regular estimations of plasma-electrolyte levels and radiological examinations of the bones for osteoporosis were not made; but when these investigations were done no abnormalities were found, thus confirming the experience of Lange et al. (1957). While on the intermittent high-dosage cortisone regimen, the children all seemed in excellent health and were remarkably free from infections. In one child (case 1) lobar pneumonia developed while she was on maintenance therapy, but this responded rapidly to penicillin, and the cortisone was not interrupted. Now, 3¼ to 4½ years after starting treatment, the children all appear well and eat normal food. Their heights and weights are within the limits of one standard deviation from the mean values for age. The blood-pressure, and blood-urea, plasma-albumin, and plasma-cholesterol levels are normal. Cases 1 and 2 show occasional traces of protein in the urine, and these children are having small doses of prednisolone (2 and 6 mg. per day respectively) continuously. The other three children (cases 3, 4, and 5) are not having hormone treatment, and since cortisone was finally withdrawn their urine has been free from protein for 30, 12, and 16 months respectively.

Discussion

Disadvantages of the intermittent high-dosage cortisone regimen are its high cost and the possibility of troublesome side-effects.

At current prices the 1200 mg. of cortisone given weekly costs some six times more than the average weekly dose of 105 mg. of prednisolone given in continuous treatment (Arneil 1958). Even if prednisolone in equivalent dosage is used instead of cortisone the cost is still more than twice as much. Moreover, the Lange regimen is continued for at least a year even if signs of nephrosis have disappeared, whereas continuous dosage may be reduced or stopped much sooner if proteinuria has ceased. Thus the total cost of intermittent high-dosage treatment may be considerably greater.

Doubt has been expressed about the safety of giving such large doses of cortisone (Kohn 1953, Rance and Chute 1955), and intermittent treatment using smaller doses of steroids has been practised in some centres (Rance and Chute 1955, Burke 1958, Kramer 1959). The Lange regimen, however, is based on doses large enough to depress antibody formation until the antigenic stimulus has disappeared, which smaller doses apparently do not achieve satisfactorily (Lange et al. 1955). Twice in the present series, because the diastolic blood-pressure was persistently above 100 mm. Hg, the daily dose of cortisone was reduced from 400 mg. to 300 mg., but this may not have been necessary, and in each case the blood-pressure fell promptly. Lange et al. (1958) also found that the systolic and diastolic blood-pressure rose by 20–30 mm. Hg in some of their patients, and returned promptly to normal after maintenance therapy was stopped. Nevertheless, hypertensive encephalopathy is a recognised hazard of steroid therapy in nephrosis (Good et al. 1957), and it is probably wise to reduce the dose if the blood-pressure is persistently high. Apart from moderate elevation of blood-pressure and slight rounding of the

face in some cases, no undesired effects were attributable to the steroid. Lange has ascribed such freedom from toxicity to the fact that treatment is intermittent.

The risk of side-effects, therefore, cannot be regarded as an objection to this form of treatment, particularly if equivalent doses of prednisolone are used, but the cost makes it necessary to show definite advantages over other schemes before advocating its general use. Even this small series shows that complete cure cannot be claimed in all cases of the nephrotic syndrome.

Lange et al. (1955) found that none of their patients relapsed while on full maintenance therapy; this was also true of these five children, although one relapsed on maintenance treatment of less than the recommended daily dose, and another relapsed while the interval between the 3-day courses was being lengthened. But Lange et al. also had no recurrences when maintenance therapy was continued for at least a year, and their experience thus differs, for two of the five patients reported here relapsed after full treatment had been given for a year or more. It is true that these five children had severe long-standing nephrosis which was resistant to ordinary treatment, and that they might have been cured by the Lange regimen if it had been instituted at the beginning of their illness, but all the same the results do not show that this method of treatment is clearly superior.

Nevertheless, these five children, who had previously been chronically ill and had spent many weeks in hospital, were able to resume normal activities and to return to school almost from starting the Lange regimen, and this in itself is a considerable achievement. All five are still leading normal lives $3^1/_4$ to $4^1/_2$ years after the start of therapy, and three of them have shown no evidence of active disease for at least a year after stopping cortisone.

A most impressive feature of the Lange regimen is the remarkable physical wellbeing of the children during maintenance therapy. Not only have they remained free from intercurrent infections which so often beset the child with nephrosis but they even seem to have escaped the ordinary respiratory infections of childhood. Their mothers and neighbours constantly remark how "radiant" they look. Moreover, their growth and development has not been retarded as may happen with continuous low-dosage regimes (Blodgett et al. 1956).

Thus the results of treatment in this small series suggest that intermittent high-dosage steroid therapy is worthy of trial in every case of nephrotic syndrome which has not responded to standard hormone treatment. Although cortisone is satisfactory, prednisolone in equivalent dosage would probably be preferable in the future.

Whether this regimen should always be used as the initial treatment is uncertain. It could be argued that it should be reserved as a second line of attack. Nevertheless, over a period of 65 months during which at least twelve deaths might have been expected, Lange et al. (1958) achieved very impressive results in forty-six patients, of whom only one died. They therefore advocate this regimen for all patients with nephrosis, and emphasise that mild nephrosis may not only become much more severe on relapse but also refractory to steroid therapy (Lange et al. 1957). I believe there is a strong case for instituting intermittent high-dosage steroid treatment from the outset in every case of nephrosis, but data from controlled comparisons in much larger series are needed to establish this beyond doubt.

Summary

Five children with the nephrotic syndrome who had not responded satisfactorily to one or more courses of hormone therapy were treated with large doses of cortisone given intermittently for long periods as advocated by Lange et al. (1953).

This treatment enabled all the children to resume their normal lives, and kept them well, without causing serious side-effects. Three have been in complete remission for 12–30 months since treatment with cortisone was stopped, but two relapsed after maintenance treatment was withdrawn.

The Lange regimen, preferably substituting prednisolone for cortisone, is recommended for all cases of nephrosis which have not responded to other schemes of treatment, and this may be the treatment of choice for every case of nephrosis in childhood.

I am grateful to Prof. J. L. Henderson for helpful advice, and to Dr. N. S. Clark for details of the further progress in case 3.

REFERENCES

Arneil, G. C. (1958) *Practitioner*, **181**, 271.
Blodgett, F. M., Burgin, L., Iezzoni, D., Gribetz, D., Talbot, N. B. (1956) *New Engl. J. Med.* **254**, 636.
Burke, E. C. (1958) *Proc. Mayo Clin.* **33**, 12.
Debré, R., Royer, P., Lévêque, B., Minor, Z. (1956) *Sem. Hôp. Paris*, **32**, 263.
Good, R. A., Vernier, R. L., Smith, R. T. (1957) *Pediatrics*, **19**, 95.
Kohn, J. L. (1953) *A.M.A. J. Dis. Child.* **86**, 479.
— (1958) *in* Proceedings of the 9th Annual Conference on the Nephrotic Syndrome (edited by Metcoff); p. 230.
Kramer, B. (1959) *Quart. Rev. Ped.* **14**, 18.
Lancet (1958) ii, 1219.
Lange, K., Slobody, L., Strang, R. (1953) *Proc. Soc. exp. Biol., N.Y.* **82**, 315.
— — — (1955) *Pediatrics*, **15**, 156.
— Strang, R., Slobody, L. B., Wenk, E. J. (1957) *A.M.A. Arch. intern. Med.* **99**, 760.
— Wasserman, E., Slobody, L. B. (1958) *J. Amer. med. Ass.* **168**, 377.
Mateer, F. M., Weigand, F. A., Greenman, L., Weber, C. J., Kunkel, G. A., Danowski, T. S. (1957) *A.M.A. J. Dis. Child.* **93**, 591.
Piel, C. F., Williams, G. F. (1957) *J. Amer. wom. Ass.* **12**, 273.
Rance, C. P., Chute, A. L. (1955) *Canad. med. Ass. J.* **73**, 959.
Vernier, R. L., Farquhar, M. G., Brunson, J. G., Good, R. A. (1958) *A.M.A. J. Dis. Child.* **96**, 306.

EPIDEMIC CONTROL OF POLIOMYELITIS WITH INACTIVE VIRUS VACCINES

STUDIES IN CYNOMOLOGUS MONKEYS

D. S. DANE
B.A., M.B. Cantab.
LECTURER IN MICROBIOLOGY

G. W. A. DICK
M.D., D.Sc. Edin., F.R.C.P.E.
PROFESSOR OF MICROBIOLOGY

With

J. J. MCALISTER, F.I.M.L.T. *and* R. T. NELSON, A.I.M.L.T.

THE QUEEN'S UNIVERSITY, BELFAST

Two doses of inactivated poliomyelitis virus vaccine (Salk type) confer about 80% protection against paralytic poliomyelitis (Medical Research Council 1957), and preliminary reports from several countries indicate that three suitably spaced doses of vaccine can give at least 90% protection. In the United States, for example, Langmuir et al. (1959) have estimated a 93% effectiveness in children up to 9 years of age and a 90% effectiveness in the 10–14 age-group, and in Canada the effectiveness of three or more inoculations has been 92% in children under 5 and 98% at ages 5–19 (Best 1959).

Although Salk's original observations showed that the antibody conversion-rate in children inoculated with a single 1 ml. dose of reference vaccine "A" was nearly 100% (Salk 1955), this does not occur with commercial batches of vaccine prepared after mid-1955. Furthermore, the injection of 1 ml. of commercial vaccine has conferred no obvious protection during the weeks following inoculation of vaccines prepared after mid-1955 (Poos and Nathanson 1956, Bundesen et al. 1957). Using vaccine prepared before mid-1955 Pope et al. (1956) claimed that 1 ml. vaccine given just before the 1955 Massachusetts epidemic was 50% effective. These differences appear to reflect the decreased potency of commercial vaccine after the introduction of manufacturing methods which

ensured greater safety. Be that as it may, the response to a single dose of vaccine is clearly related, among other things, to the amount of antigen administered.

The experiments described below were designed to show whether a single 10 ml. dose of commercial vaccine would confer protection on monkeys (cynomologus) challenged a week later with virulent type-1 poliovirus; and, if it did, whether the protection was related to the presence of demonstrable circulating antibody. Such protection would suggest that inactive poliovirus vaccines of increased potency might be effective in epidemic control and might justify the use of ten-times-concentrated commercial vaccine in children during epidemic conditions until more potent commercial vaccines were available. If the first dose provided a sufficient stimulus to antibody formation, protection against paralysis might be expected within a few days, instead of after the second dose three to four weeks later as is now the case. In face of an epidemic this gain in time would be important.

The Investigation

Materials and Methods

Tissue-culture techniques, virus isolation techniques, and serum-neutralisation tests were as previously described (Dane et al. 1957).

Virus.—Type-1 poliovirus Barr strain was isolated from a case of paralytic poliomyelitis in Belfast during 1958. Second monkey-kidney tissue-culture passage virus was used in the experiments.

Vaccine.—A British commercial formalin-inactivated poliovirus vaccine was used. The antigenic extinction limit for the type-1 component was $10^{-1\cdot2}$ estimated by Gard's method (World Health Organisation 1958). A living type-1 poliovirus (Mahoney) control with a titre of $10^{6\cdot1}TCD_{50}$ per ml. gave an antigenic extinction limit of $10^{-1\cdot6}$.

Plan of Experiment

22 adult cynomologus monkeys were divided into pairs as nearly comparable in size and general appearance as possible. Each pair was housed in one cage and individual monkeys were marked by tattooing numbers on their chests. One monkey from each cage was allocated to the " vaccine group " and the other to the " control group ". The ratio of sexes in the two groups was approximately the same. Monkeys in the vaccine group were given 10 ml. of vaccine by intramuscular injection into the right calf, and those in the control group were given 10 ml. of the tissue-culture medium in the same site.

Monkeys in both groups were at the same time given a " provoking " injection of 1 ml. procaine penicillin into the muscles of the left calf (Bodian 1956). Seven days later each monkey was challenged by the intracardiac inoculation of $10^{4\cdot7}TCD_{50}$ of type-1 poliovirus (Barr). Thereafter the monkeys were examined daily for twenty-eight days. Throat and rectal swabs were taken on three occasions during the week preceding virus inoculation and thereafter daily for fourteen days. Blood samples for antibody titrations (5–10 ml.) were taken on the day of vaccination, one week later on the day of challenge, and finally seven weeks after inoculation. In addition smaller blood samples (2 ml.) were taken every day for fourteen days after virus inoculation for virus isolation tests.

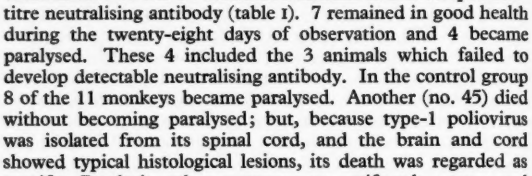
TABLE I—ANTIBODY TITRE, VIRÆMIA AND PARALYSIS IN VACCINATED AND CONTROL MONKEYS

Monkey		Antibody titre		Viræmia	Paralysis
No.	Group	7 days	7 weeks		
43	Vaccinated	Trace	<4	–	–
44	,,	8*	<4	–	–
47	,,	4	<4	–	–
49	,,	4	..	+	+
51	,,	<4	..	+	+
53	,,	6	<4	–	–
55	,,	4	45	–	–
57	,,	8	<4	–	–
59	,,	<4	..	+	+
63	,,	6	<4	–	–
65	,,	<4	..	+	+
42	Control	..	..	+	+
45	,,	..	..	+	+
46	,,	..	..	+	+
48	,,	..	<4	–	–
50	,,	..	..	+	+
52	,,	..	<4	–	–
54	,,	..	..	+	+
56	,,	..	..	+	+
58	,,	..	..	+	+
60	,,	..	..	+	+
62	,,	..	..	+	+

* Reciprocal of serum neutralising antibody versus 100 TCD_{50} of type-1 poliovirus.
All monkeys had a neutralising antibody titre of $<^1/_4$ at the start of the experiment.

Results

None of the monkeys had neutralising antibody to type-1 poliovirus at the start of the experiment. One week after vaccination 8 of the 11 vaccinated animals had developed low-titre neutralising antibody (table I). 7 remained in good health during the twenty-eight days of observation and 4 became paralysed. These 4 included the 3 animals which failed to develop detectable neutralising antibody. In the control group 8 of the 11 monkeys became paralysed. Another (no. 45) died without becoming paralysed; but, because type-1 poliovirus was isolated from its spinal cord, and the brain and cord showed typical histological lesions, its death was regarded as specific. Paralysis, when present, was uniformly severe and prostrating in monkeys of both groups, and for this reason animals were destroyed either on the day paralysis was first observed or on the day following.



+ =found dead. Death considered specific (see text).

Fig. 1—Day of onset of paralysis.

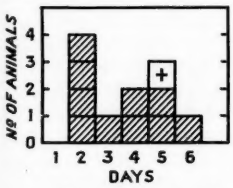
The onset of paralysis was between the seventh and seventeenth day after inoculation (see fig. 1), though monkey no. 45 was found dead on the sixth day, being apparently healthy on the fifth day. The site of first paralysis was more commonly in the legs than in the arms or face, but in all cases it extended rapidly.

Viræmia

Viræmia was found only in the monkeys which became paralysed and it lasted from two to six days (fig. 2). Every specimen of serum containing virus at the screening level of detection ($10^{1\cdot3}TCD_{50}$ per ml.) was titrated. Titres of virus ranged from this level up to $10^{3\cdot8}TCD_{50}$ per ml., the majority lying between 10^2 and $10^{3\cdot5}TCD_{50}$ per ml. All viruses isolated from serum had the cultural appearance of poliovirus, and virus in the first positive specimen from each monkey was identified serologically as type-1 poliovirus. 2 monkeys had an onset of viræmia on the day following inoculation but in the majority this occurred somewhat later and in 2 animals virus was not detected in the blood until the fourteenth day (table II). The interval between the onset of viræmia and paralysis was more uniform varying between three and eight days (fig. 3).

Virus in Throat

Type-1 poliovirus was isolated from the throat of 11 of the 13 monkeys with viræmia. Specimen collection ceased on the fourteenth day, which was the day on which viræmia was detected for the first time in the 2 remaining monkeys, and therefore virus may well have been present in their throats after this time. Poliovirus was not found in the throats of any of the 9 monkeys which remained healthy throughout the experiment.



+=monkey died in viræmic stage.

Fig. 2—Duration of viræmia.

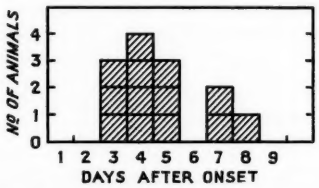
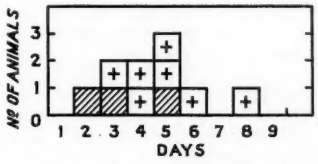


Fig. 3—Onset of paralysis in relation to onset of viræmia.



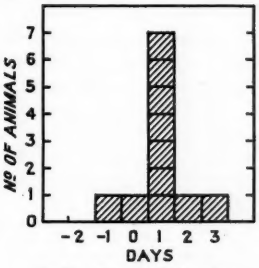
+=monkey died while excreting virus.

Fig. 4—Duration of throat virus excretion.

Monkey-kidney tissue-cultures were used for testing throat swabs, and, in all, nineteen isolations of cytopathogenic agents other than poliovirus were made. In no monkey were these agents found for more than two days, and they did not appear to influence the throat excretion of poliovirus or the course of the experiment. All isolates were serologically typed, but no quantitative measurements of virus were made. The duration of virus excretion in the throat was from two to eight days but many of the monkeys died while still excreting virus (fig. 4). The onset of throat virus excretion was related in time to the appearance of virus in the blood (fig. 5).

Virus in Gut

During the week preceding virus inoculation rectal swabs were taken on three separate occasions from each monkey and examined by inoculation into monkey-kidney tissue cultures. All the monkeys were excreting cytopathogenic agents which were not polioviruses and which were not cytopathic for HeLa cells. For this reason the rectal swabs taken after virus inoculation were tested for the presence of virus in HeLa cells. Type-1 poliovirus was isolated on only two occasions, on the tenth day from monkey no. 50 and on the eighth day from monkey no. 56. It was not possible to decide whether the presence of the other enteric viruses interfered with the growth of poliovirus in the intestinal tract; but in this experiment fæcal excretion of virus was negligible in contrast to throat excretion of virus which was regular in infected animals.



0=day of onset of viræmia.

Fig. 5—Day of onset of throat virus excretion in relation to onset of viræmia.

Antibodies

Serum from all surviving monkeys was tested for type-1 poliovirus neutralising antibody at the end of the seventh week. Virus had not been recovered from the blood, fæces, or throat of any of these animals. Monkey no. 55, however, had an antibody titre of 1/45 as opposed to a titre of 1/4 one week after vaccination. This rise in titre

TABLE II—VIRUS EXCRETION AND PARALYSIS IN MONKEYS

Animal no.	Days after inoculation																			Vaccinated
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
42	— / — / —	— / V / —	— / V / T	— / V / —	— / — / T	— / V / —	— / V / T	— / — / —	— / — / —	P / — / —	P / — / —										No
45	— / V / —	— / V / T	— / — / T	— / — / —	— / — / —																No
46	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	— / V / T	— / — / T	— / V / T	— / — / —	P / — / T	P / — / T							No
49	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / T	— / V / T	— / V / T	— / — / —	P / — / —										Yes
50	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / T	— / V / —	— / V / T	— / V / T	P / — / T											No
51	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	—	—	P	P			Yes
54	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	— / V / T	— / V / T	— / — / T	P / — / T											No
56	— / V / —	— / V / T	— / — / T	— / — / T	— / — / —	— / — / T	— / — / T	P / — / T	P / — / T												No
59	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	— / V / T	— / V / T	— / V / T	P / V / T	P / — / T										Yes
58	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	— / V / T	— / — / T	— / — / T	— / — / T	—	—	P				No
65	— / — / —	— / — / —	— / V / —	— / V / —	— / V / T	— / V / T	P / V / T														Yes
60	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	—	—	P				No
62	— / — / —	— / — / —	— / — / —	— / — / —	— / V / —	— / V / —	— / V / —	— / V / T	— / V / —	P / — / T	P / — / T										No

P=Paralysis; V=Virus in blood; T=Virus in throat; — =Tested and found negative. The animals bracketed shared cages.

suggests that the animal suffered from a type-1 poliovirus infection in spite of the fact that no virus was recovered from its blood, fæces, or throat. The failure to recover virus may have been due to the fact that the specimen collection ceased on the fourteenth day. All the other monkeys had a serum antibody titre of less than 1/4, indicating that infection had not occurred and that antibody acquired following vaccination was no longer detectable.

Discussion

4 of 11 cynomologus monkeys vaccinated with 10 ml. of commercial vaccine became paralysed after intracardiac challenge with $10^{4\cdot7}TCD_{50}$ of virulent type-1 poliovirus given one week after vaccination. By comparison the paralytic attack-rate in the control group was about twice as high, 9 out of 11 monkeys becoming paralysed. As will be discussed later, some cross-infection may have occurred between control and vaccinated monkeys. This would almost certainly have had the effect of increasing the challenge to the vaccinated monkeys, thus reducing the calculated effectiveness of the vaccine. 3 monkeys in the vaccinated group failed to develop antibody in response to vaccination and all these animals became paralysed. The 1 other paralysed monkey in the vaccinated group had low-titre antibody at the time of challenge, and, like all the other paralysed monkeys from which suitable specimens were obtained, had a viræmia and also excreted throat virus. Of the 8 which developed antibody as a result of vaccination, this was the only monkey that became paralysed. Thus among vaccinated monkeys which developed detectable antibody following vaccination there was a significantly lower incidence of paralysis than among the unvaccinated control animals (double tail $P=0{\cdot}006$).

In previous experiments we have found it difficult to induce regular alimentary infection in cynomologus monkeys by inoculating virus (type-1 Barr or Mahoney) into the stomach with a catheter. A total of 16 monkeys were inoculated with large amounts of virus in this way and only 5 developed paralysis; in addition, the results from experiment to experiment were variable. This failure to infect cynomologus monkeys regularly by stomach-tube with virulent polioviruses may have been due to interference by other enteric viruses. Perhaps a more likely explanation is that the alimentary tract of cynomologus monkeys is relatively much less susceptible to poliovirus infection than the pharynx. We are inclined to believe that the irregular and low infection-rate in cynomologus monkeys which were inoculated via the stomach was probably due to a varying degree of contamination of the pharynx with virus during passage of the catheter.

In the experiment reported above we would have preferred to challenge the monkeys by the oral route, and might have been successful in this if we had placed the virus in the mouth. However, we used the intracardiac route of inoculation because of the difficulties involved in introducing an accurate amount of virus into the mouth and because we did not realise how regularly the virus would parasitise the throats of cynomologus monkeys.

Paralysis, and in 1 monkey death without paralysis being observed, was preceded by viræmia and multiplication of virus in the throat. Throat virus was associated with viræmia, and if these were absent paralysis did not occur. In all monkeys which became paralysed and from which suitable specimens were taken, throat virus was detected. (This included all monkeys except 2 in which viræmia was not detected till the fourteenth day.) In 7 of the 11 monkeys adequately tested, throat virus was demonstrated the day after the first detection of viræmia (fig. 5). This might suggest that multiplication of virus in the throat was in general initiated as a result of viræmia. However, it must be emphasised that the method for detection of blood virus was probably 10–100 times more sensitive than could be used for throat virus. If it had been possible to use equally sensitive techniques the appearance of throat virus might have been shown to precede viræmia, and indeed this would seem quite a logical sequence of events.

Paralysis did not occur in the absence of viræmia, but all monkeys with viræmia developed a severe and prostrating paralysis. It is not possible to say whether the provocative injection of penicillin was in any way responsible for this or whether marked invasiveness was a property of the strain we used. It shows, however, that at least under certain conditions, the central nervous system of cynomologus monkeys is more susceptible to poliovirus than that of man.

Although careful precautions were taken while handling the monkeys to prevent cage-to-cage cross-infection, contact could naturally not be avoided between the monkeys caged together in pairs.

In three of eleven cages both monkeys were paralysed (nos. 50 and 51, 58 and 59, 60 and 65, see table II), and it seems unlikely that if cross-infections occurred between these monkeys they could have occurred other than by throat virus. In these three cages, each with 2 paralysed monkeys, the intervals between virus inoculation and the onset of paralysis were not outside the possible range; but the long incubation periods of seventeen days and the difference in the time of the onset of paralysis in the cage-mates make contact infections a possibility. If contact infections did occur one would expect throat virus to be present before blood virus. In fact, this was not found, but because of the lower sensitivity of the test for throat virus we cannot take the failure to isolate virus first from the throat, before its demonstration in the blood as evidence against contact infection.

The important part which throat virus seems to play in the pathogenesis of poliomyelitis in cynomologus monkeys suggests that, when considering the spread of poliovirus in man, pharyngeal virus should not be dismissed as unimportant. Although we have shown that contact infection with an attenuated poliovirus can occur between children in the absence of throat virus (Dick et al. 1957), we still think that throat virus may play an important part in the dissemination of virulent polioviruses in the community.

While our experiments with cynomologus monkeys were in progress, the antibody response of adults and children to inoculation with 10 ml. of commercial vaccine was tested by Baron et al. (1959). They showed that all of 5 non-immune adults and 5 of 7 non-immune children who were inoculated with 10 ml. of a commercial vaccine had circulating antibody to type-1 poliovirus two weeks after immunisation. The rate of conversion among the triple-negative children whom they studied (5 of 7) was similar to the rate we obtained in cynomologus monkeys (8 of 11).

Although the pathogenesis of infection in cynomologus monkeys may be different from that in humans, it seems reasonable to assume that the rapid development of low-titre antibody in children produced by a single large dose of antigen would have a protective effect against virulent virus similar to that which we have observed in cynomologus monkeys.

The practical application of these studies relates to the possibility of using more potent inactivated Salk-type vaccine (or larger doses of current commercial vaccine) in the face of an epidemic.

We consider there is evidence that low-titre circulating antibody affords protection against poliomyelitis, and that this antibody can be obtained with a single dose of inactivated vaccine, provided that the amount of antigen given is sufficient. The speed with which protection is conferred is likely to be rapid, and subsequently the normal course of injections could be given, counting the " emergency " dose as the first dose.

Summary

A proportion of cynomologus monkeys given a single 10 ml. dose of commercial poliomyelitis vaccine (Salk type) developed low-titre neutralising antibody, and these animals were protected when challenged one week later with a virulent strain of type-1 poliovirus.

Single large doses of inactivated vaccine might give useful protection in an epidemic.

In the pathogenesis of poliomyelitis in cynomologus monkeys, throat virus seems to play an important part. It may be equally important in the dissemination of the disease in man.

This investigation was supported by a grant from the National Fund for Poliomyelitis Research and the Medical Research Council.

We wish to acknowledge the assistance given by Brian McFerran, M.R.C.V.S., and James P. Evans and Laurence Corkin (student technicians) in the care and handling of the monkeys and by Mr. Fred Burns (chief technician).

REFERENCES

Baron, S., Barnett, E. V., Burch, B. L., Lynch, John M., Ehrmantraut, W. R. (1959) *New Engl. J. Med.* **260**, 966.
Best, E. W. R. (1959) Personal communication.
Bodian, D. (1956) *Amer. J. Hyg.* **64**, 92.
Bundesen, H. N., Graning, H. M., Goldberg, E. L., Bauer, F. C. (1957) *J. Amer. med. Ass.* **163**, 1604.
Dane, D. S., Dick, G. W. A., Connolly, J. H., Fisher, O. D., McKeown, F. (1957) *Brit. med. J.* i, 59.
Dick, G. W. A., Dane, D. S., Fisher, O. D., Connolly, J. H., McKeown, F. (1957) *ibid.* i, 65.
Langmuir, A. D., Alexander, E. R., Wylie, H. W., Brody, J. A. (1959) Report to American Public Health Association, Atlantic City, Oct. 20, 1959.
Medical Research Council (1957) Report to council. *Brit. med. J.* i, 1271.
Poos, R. S., Nathanson, N. (1956) *J. Amer. med. Ass.* **162**, 85.
Pope, A. S., Feemster, R. F., Rosengard, D. E., Hopkins, F. R. B., Vanadzin, B., Pattison, E. W. (1956) *New Engl. J. Med.* **254**, 110.
Salk, J. E. (1955) *J. Amer. med. Ass.* **158**, 1239.
World Health Organisation (1958) *Tech. Rep. Wld Hlth Org.* no. 145.

X-RAY STUDY OF PASSAGE OF AIR THROUGH THE PHARYNX IN ANÆSTHETISED PATIENTS

H. RUBEN
Cand. Med. Copenhagen
DIRECTOR, ANÆSTHESIA DEPARTMENT

N. BENTZEN
Cand. Med. Copenhagen
FIRST ASSISTANT, RADIOLOGY DEPARTMENT

FINSEN INSTITUTE, COPENHAGEN

S. K. SAEV
M.D. Sofia
WORLD HEALTH ORGANISATION FELLOW, ANÆSTHESIOLOGY CENTRE, COPENHAGEN

THIS investigation was performed to establish the influence of the position of the head and jaw on the patency of the air-passage at the level of the tongue. 21 patients, all under general anæsthesia before operation, curarised, and deeply relaxed and apnœic, were examined radiographically in the supine position. 12 of the 21 were similarly examined when awake.

Method

12 patients had lateral views taken in the following three positions during anæsthesia and when awake: (1) with the head tilted back by maximal extension in the upper part of the cervical spine; (2) with the head in normal position (i.e. with the pupil axis vertical) without attempt to extend or flex the neck; (3) with the neck flexed, the head supported by a pillow 8 cm. high.

In a deeply relaxed patient the mouth opens during maximal backward tilting of the head because of the pull of the tissues in front of the neck. In 10 patients radiographs were taken when, during the backward tilting, the patient's mouth was closed by pushing up the chin in the midline.

11 patients had lateral views taken with the head tilted backwards by extension in the uppermost part of the cervical spine, and additionally during application of the following 3 manœuvres: (1) the mouth closed by pushing the chin up against the maxilla; (2) the mandible pushed forwards by pressure applied forcefully on both sides behind the ramus of the mandible; (3) the mandible pulled forwards forcefully with a finger in the patient's mouth behind his lower front teeth.

To find out the importance of extension itself, in 6 patients radiographs were taken during these same three manœuvres, but with the patient's head in the normal position.

Finally, in a few cases X-rays were taken during anæsthesia with the patient's head hanging over the edge of the operating-table.

Results

The results are shown in the accompanying table. The distances between the pharyngeal wall and the back of the tongue, and between the pharyngeal wall and the epiglottis, are in each case the smallest clearances seen. As the front-back clearance (unlike the transversal clearance) varies substantially, this clearance is taken as an expression of the patency of the pharynx.

In this account *complete obstruction* denotes that no air space at all was seen on the X-ray picture between the pharyngeal wall and the tongue. *Partial obstruction* denotes that the clearance was at most 3 mm.; *satisfactory air-passage* that there was clearance of 5–6 mm., and a *very good air-passage* that there was a 7 mm. or larger clearance. 5 mm. was chosen as indicating satisfactory air-passage because this was the smallest clearance found in any awake patient in this study.

With the *patients awake* there was in every instance a clearance of 5–20 mm. at the levels of the tongue and the epiglottis. Usually it was slightly smaller when the head was tilted forwards than in the normal position. When the head was extended there was in every instance an increase in the clearance both at the tongue and at the epiglottic level of the pharynx, the clearances varying between 8 and 25 mm.

Of the 12 *anæsthetised patients* with the *head flexed*, at the level of the tongue complete obstruction was found in 8 cases, and partial obstruction in 2 cases. With the head in the normal position complete obstruction was found in 4 of 12 cases, and partial obstruction in a further 4. Clinically, therefore, one might expect to find obstruction at the tongue in 10 out of 12 cases when the head is flexed, and in 8 out of 12 cases when the head is in the normal position. In only 1 case was a satisfactory air-passage found at the tongue in both the flexed and the normal positions. At the epiglottic level, with the head flexed, no clearance was found in 8 cases and a clearance of only 2 mm. or less in the other 4 cases. With the head in the normal position no air space was seen in 4 cases, and an air space of 3 mm. or less in 6 cases.

With the head of the anæsthetised patient tilted back,

CLEARANCES (MM.) BETWEEN PHARYNGEAL WALL AND TONGUE, AND BETWEEN PHARYNGEAL WALL AND EPIGLOTTIS

Case no.	Sex	Age (yr.)	Height (cm.)	Body-weight (kg.)	Dental state	Patients awake						Patients anæsthetised																	
						Clearance at tongue with head:			Clearance at epiglottis with head:			Clearance at tongue									Clearance at epiglottis								
												Position of head			Position of mandible						Position of head			Position of mandible					
						Flexed	Normal	Backwards	Flexed	Normal	Backwards	Flexed	Normal	Backwards	a[1]	b[1]	c[1]	a[2]	b[2]	c[2]	Flexed	Normal	Backwards	a[1]	b[1]	c[1]	a[2]	b[2]	c[2]
1	M	31	170	62	+T	7	6	18	5	5	12	2	5	15	..	..	..	25	..	..	0	2	15	..	..	..	20	..	..
2	F	64	151	73	+T	6	15	18	6	8	12	0	5	6	..	..	..	..	..	..	0	3	8	..	..	..	..	..	..
3	F	29	168	47	+T	9	10	20	5	6	8	0	2	9	..	..	..	..	..	..	0	2	10	..	..	..	..	..	..
4	F	62	157	59	−T	10	13	20	6	6	10	0	0	12	..	..	..	25	..	..	0	2	8	..	..	..	25	..	..
5	F	69	152	58	−T	10	11	20	7	5	11	0	1	5	..	..	..	19	..	..	0	0	5	..	..	..	26	..	..
6	F	53	..	..	+T	18	14	22	20	7	17	0	0	10	..	..	..	15	..	..	2	2	14	..	..	..	23	..	..
7	F	61	155	72	−T	15	19	25	11	15	20	0	0	10	..	..	..	25	..	..	0	0	9	..	..	..	25	..	..
8	M	69	..	..	−T	19	20	20	6	10	15	9	10	10	..	..	..	20	..	..	2	5	12	..	..	..	27	..	..
9	F	52	156	60	−T	11	12	25	5	6	17	3	0	8	..	..	..	20	..	..	1	0	10	..	..	..	30	..	..
10	M	66	170	51	−T	13	12	15	6	10	10	5	5	6	..	..	..	10	..	..	2	6	10	..	..	..	23	..	..
11	M	50	170	70	−T	..	..	..	..	..	..	..	..	..	..	..	..	15	25	23	..	..	..	..	..	..	20	33	27
12	F	63	175	47	+T	..	..	..	..	..	..	..	..	..	..	..	..	22	32	32	..	..	..	..	..	..	24	32	29
13	M	48	186	90	+T	..	..	..	..	..	..	..	..	..	..	..	..	14	15	20	..	..	..	..	..	..	15	19	24
14	F	55	157	57	−T	..	..	..	..	..	..	..	..	..	..	..	..	22	25	25	..	..	..	..	..	..	30	30	30
15	F	63	164	60	−T	..	..	..	..	..	..	..	..	..	..	..	..	25	25	15	..	..	..	..	..	..	20	20	15
16	F	50	164	72	+T	..	..	..	..	..	..	..	..	..	8	11	15	15	20	23	..	..	..	10	15	10	15	25	25
17	F	69	160	58	−T	..	..	..	..	..	..	..	..	..	15	13	12	16	19	20	..	..	..	20	18	18	25	19	22
18	M	67	172	52	−T	..	..	..	..	..	..	..	..	..	20	30	28	30	35	40	..	..	..	23	28	31	35	40	42
19	F	68	165	58	+T	..	..	..	..	..	..	..	..	..	10	25	20	19	35	38	..	..	..	10	25	18	20	35	24
20	M	81	170	62	−T	5	14	18	5	5	9	0	3	5	15	15	15	15	12	15	0	3	5	15	12	10	15	15	10
21	F	46	158	51	+T	10	9	19	5	5	15	0	1	8	12	25	15	17	25	22	0	0	6	14	22	12	22	23	22
				Averages ..		11	13	20	7	7	13	2	3	9	13	20	17	19	24	26	1	2	9	15	20	17	23	26	25

a, mouth closed by pushing chin up.
b, mandible pushed forwards by pressure behind each ramus.
c, mandible pulled forwards with thumb in mouth behind lower front teeth.
1, head in normal position.
2, head tilted back maximally.

a patent air-passage was found in every instance; in 8 of the 12 cases the air-passage was very good and in 4 cases satisfactory. When, with the head in this extended position, the chin was pushed up so that the mouth was closed, this usually increased the clearance notably: in 10 of the 12 cases it was then even larger than, and in 2 cases about the same as, in the same patient when awake with the head in the normal position. In the extended position a larger clearance was always found at the epiglottis than at the tongue.

In 11 of the patients, in whom the effect of different mandible manœuvres with the head in the extended position was compared, this effect agreed with that found in 8 other patients in this investigation: closing the mouth notably enlarged the clearance between the pharyngeal wall and the tongue and between the pharyngeal wall and the epiglottis. Pulling forwards the body of the mandible or pushing forwards the ramus of the mandible at each side usually, but not in every case, gave a larger clearance than did the combined manœuvre of extension and pushing the jaw up against the maxilla. This was so, however, only when with the forward displacement of the jaw the head was tilted maximally back; otherwise the clearance was much the same with all these manœuvres.

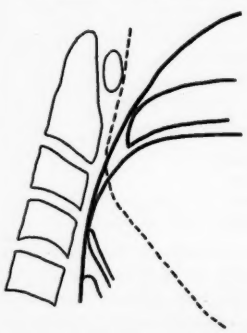
Fig. 1—Anæsthetised patient: head flexed; no clearance between tongue, epiglottis, and pharyngeal wall.

Air-passage at Soft Palate

In 10 *waking patients* the air-passage between the soft palate and the tongue, and between the soft palate and the pharyngeal wall, was examined. In 9 of the 10 patients no air space was seen between the tongue and the palate, an in 1 case no air space between the palate and the pharynx.

Of the 19 *anæsthetised patients* in the extended position with the jaw pushed up, in 5 there was no air space between the soft palate and the pharyngeal wall, and in 6 no air space between the soft palate and the tongue.

Between the palate and the pharynx no air space was seen in 3 out of 11 cases when the mandible was pushed forwards behind the ramus, and in 4 of these 11 when the body of the mandible was pulled forwards. Between the palate and the tongue, and between the palate and the pharynx, no air space was seen in 1 case and in no case, respectively.



Discussion

This study shows clearly that the position of the head is important for the

patency of the air-passage through the pharynx. While in all the waking patients there was an open air-passage independently of the position of the head, this was not so in the anæsthetised, curarised patients. With the head in the flexed position obstruction was found in almost all the patients. Of 12 patients the only 2 who then showed an open air-passage at the tongue level showed no air space at the epiglottis. With the head in the normal position only 2 of the 12 patients showed an open air-passage at the tongue as well as the epiglottis; 2 more showed a small clearance at the epiglottis, but none at the tongue; and in 8 no air space could be observed at the tongue or at the epiglottis.

With the head extended each of the 12 anæsthetised patients showed a satisfactory air-passage; and in 7 of these it was very good both at the tongue and at the epiglottis. With the head in the hanging position an air passage was produced only if the backward tilt resulted in extension of the upper part of the cervical spine; extension of the lower part alone did not have this result.

Fig. 2—Anæsthetised patient: head tilted maximally back; air-passage patent.

Tilting the head back, and in addition closing the mouth by pushing the jaw up against the maxilla, substantially increased the clearance at the epiglottis and at the tongue level; in each of 19 patients very good clearance was found during this combined manœuvre. The clearance thus produced was even larger with the patient under anæsthesia than when awake with the head in normal position.

Before and in the intervals between radiography the patients were ventilated with bag and mask, keeping the head tilted back and the chin pushed up. At these times there was clinically in every case an open air-passage, even where the radiographs showed no air space between the soft palate and the tongue or between the soft palate and the pharynx. It therefore seems that this finding has no practical importance. The reason for the discrepancy is probably that the pliable soft palate is moved out of the stream by the moving air.

Extension of the head with closure of the mouth was found to give practically the same opening of the air-passage as pulling or pushing the mandible forwards with the head kept in the normal position. Even when the head was tilted maximally back, the clearances found were only some 25% greater with forward displacement of the jaw. Independently of which technique was used, the clearance established was always greater than the front-back clearance seen in the larynx; so with the respiratory rates normally existing, these relatively minor variations could probably be considered as of no practical importance.

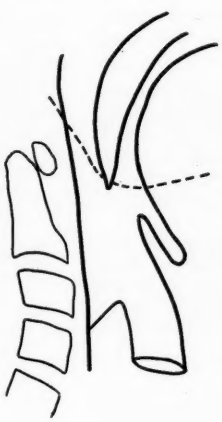


Fig. 3—Anæsthetised patient: head tilted back and mouth closed by pushing chin up; much increased clearance compared with backward tilt only.

Conclusions

In the unconscious patient the air-passage through the pharynx is usually maintained by moving the mandible forwards. This study has shown that patency is obtained by merely tilting the head back, thereby producing extension of the upper part of the cervical spine. When, in addition, the patient's mouth is closed, clearance is substantially increased, making a very good air-passage. Application of these manœuvres to anæsthetised patients, during spontaneous respiration as well as during apnœa, has shown this

method to be effective clinically; and it has proved of practical importance when using a facemask during anæsthesia. It has also been used during expired-air resuscitation, when it was found that laymen more easily learnt this technique than that of the usual forward displacement of the jaw.

VENOARTERIAL SHUNTS IN CIRRHOSIS OF THE LIVER

JOHAN GEORG
M.D. Copenhagen

KRESTEN MELLEMGAARD
Cand. Med. Copenhagen

NIELS TYGSTRUP
Cand. Med. Copenhagen

KJELD WINKLER
Cand. Med. Copenhagen

From Rigshospitalet, Copenhagen

CYANOSIS and clubbed fingers have occasionally been noted in patients who have cirrhosis of the liver but no demonstrable disease of heart or lung. Snell (1935) and Keys and Snell (1938) were the first to demonstrate a decrease of arterial oxygen saturation in cirrhosis, finding it in 48 of 61 cases. Later workers have observed this decrease with varying frequency, but generally much less often (Darling, 1940, Claypool et al. 1957, Murray et al. 1958). In 28 consecutive cases investigated by us the oxygen saturation was below 93% on one or more occasions in 14.

The aim of the present study was to ascertain whether venoarterial shunting of blood is a cause of this arterial unsaturation.

Methods

In 19 patients admitted to medical department B of Rigshospitalet, the diagnosis of cirrhosis was established clinically and by laboratory tests, being confirmed histologically (liver biopsy or necropsy) in 18. Only 3 had chronic alcoholism. In the 9 subjected to cardiac catheterisation normal findings were recorded in the hearts.

For comparison, 17 patients without signs of hepatic, cardiac, or pulmonary disease were studied, 4 of them having cardiac catheterisation.

The examination was made in the fasting state, with the patient supine. Blood was collected in oiled heparinised syringes from an indwelling arterial needle. The patient then breathed pure oxygen, or 50% oxygen in nitrogen, for twenty minutes, after which blood was again collected. Expired air was sampled for oxygen and carbon-dioxide content before and during the inhalation of oxygen.

The patients subjected to cardiac catheterisation were premedicated with phenobarbitone 200 mg. Blood was drawn from the pulmonary artery simultaneously with the arterial sampling. For assessment of the degree of portal hypertension, wedged hepatic venous pressure was obtained before the inhalation of oxygen.

Analytical Procedures

The oxygen tension was measured polarographically with a dropping mercury electrode (Bartels 1951, Bartels and Laue 1951). Each result given is the average of three separate determinations. Individual calibration curves were produced by equilibrating blood from each patient for twenty minutes with three gas mixtures containing varying amounts of oxygen and nitrogen, and 5% carbon dioxide. The coefficient of variation of the method is about 2% at physiological oxygen tensions and about 4% at high tensions.

The carbon-dioxide tension of the samples was calculated from determinations of pH of the blood before and after equilibration with carbon dioxide at a tension of 40 mm. Hg (Astrup 1957).

Oxygen saturation was determined with the Brinkman hæmoreflector (Zijlstra 1953), and oxygen content was calculated from oxygen saturation and from oxygen capacity (derived from a photometric determination of the hæmoglobin concentration).

Gas analysis was performed on the Haldane apparatus.

Calculation

For calculations of the venoarterial shunt the following equation was used (cf. Comroe et al. 1955):

$$\frac{Q_S}{Q} = \frac{C_{\acute{c}O_2} - C_{aO_2}}{C_{\acute{c}O_2} - C_{\bar{v}O_2}}$$

where

$\frac{Q_S}{Q}$ = ratio of venoarterial shunt to cardiac output

$C_{\acute{c}O_2}$ = oxygen content of pulmonary end-capillary blood.

This last value is derived from the alveolar oxygen tension, which during oxygen inhalation is considered identical with the end-capillary oxygen tension. The alveolar oxygen tension is calculated from the Bohr equation, taking arterial carbon-dioxide tension as representing mean alveolar carbon-dioxide tension.

C_{aO_2} = oxygen content of arterial blood (oxygen capacity plus physically dissolved oxygen)

$C_{\bar{v}O_2}$ = oxygen content of mixed venous blood

The oxygen content of mixed venous blood was measured during cardiac catheterisation or estimated from an assumed arteriovenous oxygen difference of 4·5 vol. %.

Results

Estimation of venoarterial shunt in the 17 control patients (table I) shows an average value of 2·5% of the cardiac output, with a standard deviation of 1·6%. This, according to the *t* test, signifies that 95% of normal subjects will have shunts below 6%. These values agree well with those in the literature.

Table II shows that 12 of the 19 patients with cirrhosis had venoarterial shunts above the value regarded as the upper limit of normal.

In the first part of table II, comprising patients subjected to cardiac catheterisation, two values of the relative venoarterial shunt are listed, one based on the measured arteriovenous oxygen difference, the other on an estimated difference of 4·5 vol. %, which is used in the patients not catheterised. As the arteriovenous oxygen difference in cirrhosis of the liver is often below this " normal " value, because of increased cardiac output, the shunts recorded in the second part of table II—from patients not catheterised—tend to be minimal values.

In our experience the degree of arterial unsaturation in

TABLE I—DATA FROM 17 NORMAL SUBJECTS

paO_2, oxygen tension of arterial blood.
A.A.D., alveolar-arterial oxygen tension difference.
A.V.D., arteriovenous oxygen difference.
C.O., cardiac output.

Sex and age	Respiration in air				Respiration in oxygen			Shunt %	
	paO_2 (mm. Hg)	A.A.D. (mm. Hg)	A.V.D. (vol.* %)	C.O. (l. per min.)	paO_2 (mm. Hg)	A.A.D. (mm. Hg)	A.V.D. (vol. %)	Actual A.V.D.	A.V.D. (4·5 vol %)
M 17	101	4	3·7	3·27	650	8	4·1	1	1
F 16	100	5	2·7	5·74	608	34	2·9	3	2
F 17	103	4	3·3	6·27	613	39	3·7	3	3
M 16	102	8	4·5	..	284•	44	5·2	2	3
M 55	90	21	..	..	655	21	..	..	1
M 23	102	6	..	..	666	5	..	..	0
F 40	101	6	..	..	618	38	..	..	2
M 19	101	5	..	..	608	46	..	..	3
M 34	97	11	..	..	597	61	..	..	4
M 51	89	15	..	..	582	77	..	..	5
M 62	96	17	..	..	645	37	..	..	2
M 20	95	13	..	..	619	50	..	..	3
M 44	100	13	..	..	608	76	..	..	5
M 23	109	3	..	..	676	5	..	..	0
M 9	98	10	..	..	276•	50	..	..	3
M 17	106	5	..	..	645	28	..	..	2
M 20	98	7	..	..	624	46	..	..	3
Mean	99	9				39			2·5
Range	89–106	4–21				5–77			0–5
S.D.	5	5				21			1·5

• Values obtained during respiration in 50% oxygen.

TABLE II—DATA FROM 19 PATIENTS WITH LIVER CIRRHOSIS

Patient	Respiration in air				Respiration in oxygen			Shunt %	
	paO_2 (mm. Hg)	A.A.D. (mm. Hg)	A.V.D. (vol. %)	C.O. (l. per min.)	paO_2 (mm. Hg)	A.A.D. (mm. Hg)	A.V.D. (vol. %)	Actual A.V.D.	A.V.D. (4·5 vol. %)
1	70	36	4·6	3·74	387	279	6·1	12	16
2	92	17	2·6	7·92	508	149	3·2	10	9
3	94	14	3·4	4·18	582	79	..	..	5
4	95	13	1·7	12·9	482	190	1·6	26	11
5	..	..	4·2	4·98	539	120	4·0	8	7
6	89	20	3·5	5·12	492	173	3·3	14	10
7	94	16	5·4	5·48	503	185	6·2	8	11
8	82	24	5·3	3·77	300*	33	5·1	2	2
9	100	8	4·9	5·30	287*	22	4·7	1	1
10	36	70	..	..	59	591	..	..	42
11	84	24	..	..	434	227	..	..	13
12	101	6	..	..	619	34	..	..	2
13	83	24	..	..	524	152	..	..	9
14	92	18	..	..	243*	72	..	..	5
15	71	37	..	..	177*	149	..	..	10
16	84	8	..	..	403†	64	..	..	4
17	91	20	..	..	420†	62	..	..	4
18	84	27	..	..	503	169	..	..	10
19	82	21	..	..	518	144	..	..	9
Mean	84	22				152			9·5
Range	36–101	6–70				22–591			1–42

* Values obtained during respiration in 50% oxygen.
† Values obtained during respiration in 70% oxygen.

cirrhosis shows great fluctuation. Whether the same is true of the venoarterial shunt cannot be stated with certainty, but the few repeated shunt determinations—generally performed after an interval of several months—have shown remarkably constant values.

None of the clinical and laboratory data in table III can be correlated with the presence or magnitude of an abnormal venoarterial shunt.

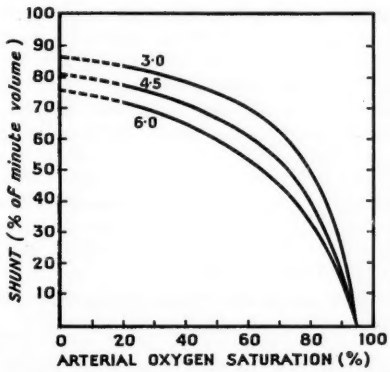
Discussion

The alveoloarterial oxygen gradient, existing during respiration in atmospheric air, may be due to uneven distribution of the inspired air to different parts of the lungs (resulting in regional hypoventilation), to difficulties in diffusion, or to venoarterial shunt. During respiration in oxygen the distribution and diffusion factors are eliminated, and if there is still an alveoloarterial oxygen gradient it must be due to a venoarterial shunt.

The pioneer work on the present method of shunt estimation was done by Berggren (1942) and the method has been used extensively by Bartels and his associates (Bartels et al. 1955, Rodewald et al. 1956). Wilson et al. (1953) using Berggren's method, noted an average shunt of 5·8% (standard deviation 2·9%) in 10 patients with cirrhosis.

The observation of cyanosis and clubbing of the fingers in this disease goes back to Flückiger (1884), followed by Gilbert and Fournier (1895), Boutron (1899), Hijmans van den Bergh (1901), and Gilbert and Lereboullet (1902). It was made chiefly in cases of biliary cirrhosis or juvenile cirrhosis.

The observed high incidence of abnormal venoarterial shunts in cirrhosis indicates that this is an essential factor in the arterial unsaturation previously noted in this disease. Our data do not permit a definite quantitative evaluation. Only fairly large shunts can reduce the arterial oxygen saturation significantly, as depicted in the chart, which shows the calculated effect of veno-



Influence of venous-to-arterial shunt on the oxygen saturation of the arterial blood.

The curves are calculated assuming a constant cardiac output and arteriovenous oxygen difference (3·0, 4·5, or 6·0 vol. %), and an arterial oxygen saturation of 95% initially.

arterial shunting on the arterial oxygen saturation in a patient with an oxygen capacity of 20 vol. % and initially 95% arterial oxygen saturation, and a constant cardiac output. Abnormal oxygen dissociation for the hæmoglobin of patients with cirrhosis was demonstrated by Keys and Snell (1938). This may contribute to the arterial oxygen unsaturation, but in most cases a venoarterial shunt seems to be a sufficient explanation.

The location of the shunt is uncertain. Atelectasis of the lungs, caused, for example, by pleural effusion or ascites, will result in venoarterial shunting (i.e., perfusion of unventilated parts of the lungs); but in our material (table III) such features have not been prominent.

TABLE III—CLINICAL DATA OF THE 19 PATIENTS

Patient	Sex and age	Ætiology	Approx. duration (years)	Spider nævi	Palmar erythema	Ascites	X-ray of lungs	X-ray of œsophagus	Wedged hepatic or splenic pressure (mm. Hg)
1	F 49	Unknown	4	0	(+)	0 ..	Normal	Normal	12
2	F 53	Hepatitis	3	+	+	0	,,	Varices	32
3	F 58	Unknown	2	0	0	0	,,	Normal	23
4	M 53	Alcoholic	6	++	+	+	,,	Varices?	31
5	F 52	Unknown	7	(+)	0	0	Pleural changes	Varices	12
6	F 64	Unknown	4	(+)	0	0	Normal	Normal	16
7	M 75	Unknown	1	0	0	(+)	Pleural changes	,,	19
8	F 55	Unknown	?	0	0	0	Pulmonary cysts	,,	15
9	M 55	Hepatitis	1½	0	+	0	Normal	,,	14
10	M 60	Alcoholic	5	++	++	+	Diffuse infiltrates	Varices?	20
11	F 29	Hepatitis	9	(+)	(+)	0	Normal	Normal	..
12	F 54	Hepatitis	8	0	0	0	,,	,,	14
13	F 60	Unknown	6	0	0	0	,,	,,	10
14	M 75	Hepatitis	1	+	+	+	Pleural changes	,,	21
15	M 59	Alcoholic	½	0	+	++	Small atelectases	,,	27
16	F 53	Unknown	3	0	0	0	Normal	Varices?	12
17	F 32	Unknown	1½	(+)	(+)	0	,,	Normal	17
18	F 71	Unknown	3	0	0	0	,,	,,	12
19	F 56	Unknown	6	(+)	(+)	0	Slight effusion?	Varices?	20

Rydell and Hofbauer (1956) demonstrated venoarterial shunts by postmortem casts of the pulmonary vessels in a patient with juvenile cirrhosis. This patient was found to have numerous minute arteriovenous anastomoses in the lungs, and these were regarded as pulmonary spider nævi. Hales (1956), using a similar technique, also demonstrated pulmonary arteriovenous fistulæ in a patient with cirrhosis, but he regarded these as evidence of Rendu-Osler-Weber disease, in which pulmonary arteriovenous anastomoses are common and may be demonstrated by pulmonary angiography. This technique failed to reveal any abnormality in 2 cases of cirrhosis studied by Murray et al. (1958), and in one of our cases (no. 10). This patient, who had the biggest shunt of the series, died later in the hospital. No casts were made, but on routine examination the lungs appeared normal macroscopically and histologically.

Another cause of venoarterial admixture was demonstrated by Calabresi and Abelmann (1957) and by Schoenmackers and Vieten (1957). By postmortem injection they demonstrated abnormal communications from the portal vein via the periœsophageal and mediastinal veins to the bronchial and pulmonary veins. These anastomoses are presumably pre-existing channels which the portal hypertension brings into use.

This appears to be the most likely explanation of the arterial unsaturation in patients with cirrhosis. In this respect determination of venoarterial shunts in patients with portal hypertension from extrahepatic causes will be particularly interesting. It should be noted that the size of a shunt through these channels is underestimated with the method we used, because the oxygen saturation of the blood from the portal vein tends to be higher than that of the mixed venous blood from the right heart.

Summary

Venoarterial shunt has been estimated in 19 patients with cirrhosis of the liver, using polarographic measurement of arterial oxygen tension during oxygen breathing. The shunts averaged 9·5% of the cardiac output, and were in 12 cases found to be above the 6% that is regarded as the upper normal limit with the present technique.

The heart catheterisations were performed in the cardiological laboratory of medical department B, Rigshospitalet. We wish to thank Prof. Erik Warburg and Dr. A. Tybjærg Hansen for their help and advice.

REFERENCES

Astrup, P. (1957) *Scand. J. clin. lab. Invest.* **8**, 33.
Bartels, H. (1951) *Arch. ges. Physiol.* **254**, 17.
— Laue, D. (1951) *ibid.* p. 126.
— Beer, R., Fleischer, E., Hoffheinz, H. J., Krall, J., Rodewald, G., Wenner, J., Witt, I. (1955) *ibid.* **261**, 99.
Berggren, S. (1942) *Acta physiol. scand.* Suppl. 11, p. 1.
Boutron, R. (1899) Du doigt hippocratique dans les cirrhoses biliaires. Paris.
Calabresi, P., Abelmann, W. H. (1957) *J. clin. Invest.* **36**, 1257.
Claypool, J. G., Delp, M., Lin, T. K. (1957) *Amer. J. med. Sci.* **234**, 48.
Comroe, J. H., Forster, R. E., DuBois, A. B., Briscoe, W. A., Carlsen, E. (1955) The Lung. Chicago.
Darling, R. C. (1940) *Ann. intern. Med.* **14**, 898.
Flückiger, M. (1884) *Wien. med. Wschr.* **34**, 1458.
Gilbert, A., Fournier, L. (1895) *C.R. Soc. Biol., Paris*, **47**, 419.
— Lereboullet, P. (1902) *Gaz. hebd. Med. Chir.* **49**, 1.
Hales, M. R. (1956) *Amer. J. Path.* **32**, 927.
Hijmans van den Bergh, A. A. (1901) *Ned. Tijdschr. Geneesk.* **45**, 761.
Keys, A., Snell, A. M. (1938) *J. clin. Invest.* **17**, 59.
Murray, J. F., Dawson, A. M., Sherlock, S. (1958) *Amer. J. Med.* **24**, 358.
Rodewald, G., Bartels, H., Beer, R., Fleischer, E., Hoffheinz, H. J., Krall, J., Wenner, J., Witt, I. (1956) *Z. ges. exp. Med.* **126**, 565.
Rydell, R., Hofbauer, F. W. (1956) *Amer. J. Med.* **21**, 450.
Schoenmackers, J., Vieten, H. (1957) *Arch. Kreislaufforsch.* **25**, 222.
Snell, A. M. (1935) *Ann. intern. Med.* **9**, 690.
Wilson, R. H., Ebert, R. V., Borden, C. W., Pearson, R. T., Johnson, R. S., Falk, A., Dempsey, M. E. (1953) *Amer. Rev. Tuberc.* **68**, 177.
Zijlstra, W. G. (1953) Fundamentals and Applications of Clinical Oximetry. Assen, Netherlands.

EFFECT OF CORTISONE ON THE EXCRETION OF ALDOSTERONE IN VIRILISING ADRENAL HYPERPLASIA

J. DE GRAEFF, M.D. Leiden
A. J. MOOLENAAR, D.Sc. Leiden

From the Department for Clinical Endocrinology and Diseases of Metabolism, University Hospital, Leiden, Holland

IN 1955 Prader et al. reported a raised level of aldosterone in the urine of some patients with the adrenogenital syndrome caused by congenital adrenal hyperplasia (" virilising adrenal hyperplasia "). In 1959 Blizzard et al. published measurements of aldosterone excretion in a large number of patients with virilising adrenal hyperplasia. They found normal or large amounts of aldosterone in the urine of those without associated salt-loss, but little or no aldosterone in the urine of those with a salt-losing syndrome.

As no data seem to be available on the influence of cortisone on aldosterone excretion in this syndrome, we describe and discuss here the results of a study made in 1956 (de Graeff and Moolenaar 1957).

Investigation

Patient A, aged 14, was a typical case of virilising adrenal hyperplasia in the female. A laparotomy in 1947 had demonstrated a uterus and ovaries. Patient B, aged 8, was a typical case of this disorder in the male, presenting as macrogenitosomia præcox. Neither patient had ever displayed the salt-losing syndrome.

Aldosterone excretion was measured by the method of Moolenaar (1957) (normal values 2–12 μg. per day). Neutral 17-ketosteroids were measured by the method of Kassenaar et al. (1950). Otherwise routine laboratory methods were used. Patient A received a constant diet, containing a calculated daily amount of 175 mEq. of sodium and 90 mEq. of potassium. Patient B did not receive a constant diet, because lack of cooperation made this impossible.

The excretion of neutral 17-ketosteroids and aldosterone was measured at intervals. In patient A the urine was collected daily, and the excretion of sodium and potassium was measured throughout the study.

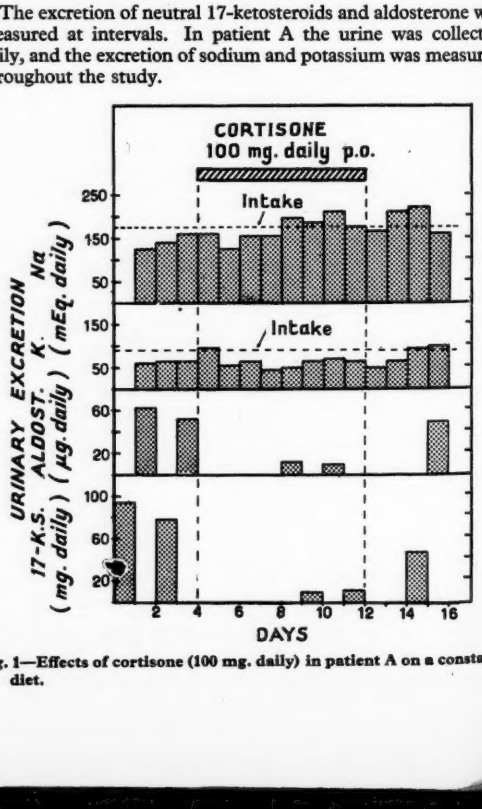


Fig. 1—Effects of cortisone (100 mg. daily) in patient A on a constant diet.

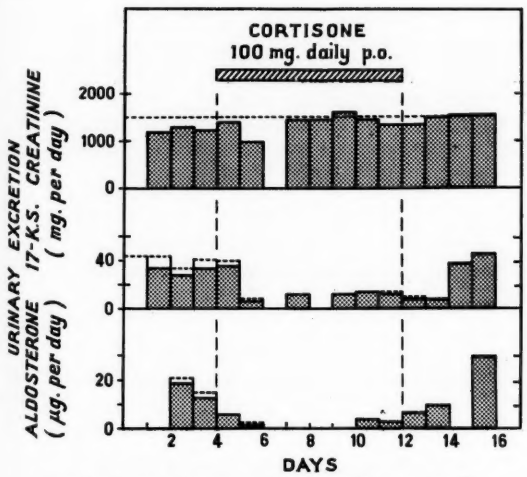


Fig. 2—Effects of cortisone (100 mg. daily) in patient B.

According to the level of creatinine excretion in the urine not all urinary collections appear to have been complete. The amounts of neutral 17-ketosteroids and aldosterone in the urine have been corrected for this (interrupted lines), taking an average daily amount of 1500 mg. of creatinine as normal for this patient.

Both patients received 100 mg. of cortisone by mouth, divided into four equal doses, daily for 8 days.

As would be expected, their excretion of neutral 17-ketosteroids fell to normal. After cessation of cortisone administration the excretion of 17-ketosteroids returned to pre-treatment levels in patient B, and rose significantly in patient A within 2 days.

Patient A excreted very large amounts of aldosterone (62 and 51 μg. per day) at the beginning of the study. During the administration of cortisone high normal values (12 and 10 μg.) on the 6th and 8th day were obtained. On the 3rd day after stopping the treatment the high value of 50 μg. was found again (fig. 1).

In patient B the excretion of aldosterone was moderately raised (18 and 13 μg. per day) before cortisone was given. It fell to a low normal level within 2 days of commencement of cortisone treatment (2 μg. per day) and remained there till cortisone treatment was stopped (fig. 2). It then rose again, reaching a high level (28 μg. per day) on the 4th day. The fact that, judging by creatinine excretion, not all urinary collections were complete does not invalidate this statement.

The data on the excretion of sodium and potassium in patient A are rather inconsistent. There was perhaps a small increase in the amount of urinary sodium towards the end of the cortisone period, but this persisted after administration of cortisone was stopped. The excretion of potassium was more or less constant, with a small peak on the first day of cortisone administration and a small increase 3 days after this ceased.

Neither patient showed any clinical changes, subjective or objective, during the administration of cortisone.

Discussion

The two patients both excreted abnormally large amounts of aldosterone on a normal salt intake, and there seems to be no doubt that cortisone reduced their aldosterone excretion to normal levels.

In four patients without associated salt-loss, Blizzard et al. (1959) did not find that cortisone reduced aldosterone excretion; but, as they do not give any pre-treatment values, no definite conclusions can be reached.

Assuming that urinary aldosterone levels reflect the rate of secretion of this hormone, the effect of cortisone on aldosterone excretion can be explained in two ways.

Crigler et al. (1952) have suggested that in patients with virilising adrenal hyperplasia there is a "sodium-losing" factor, which is corticotrophin-dependent. The loss of sodium and thus of extracellular fluid would be a stimulus to aldosterone secretion, increase of which would counteract the sodium-losing factor. On this hypothesis, proposed by Prader et al. (1955), a patient with a salt-losing syndrome would be "uncompensated" whereas a patient without salt-loss would be compensated. This would explain why some patients have a salt-losing syndrome in their youth but seem to overcome this later. Our two patients might then be regarded as compensated cases. Cortisone, by inhibiting the secretion of corticotrophin, would reduce the production of the salt-losing factor, thus removing the stimulus for increased aldosterone secretion. It is difficult to say what would happen to sodium and potassium excretion in such circumstances. The decrease in the effect of the salt-losing factor would tend to inhibit sodium excretion, but the fall in aldosterone secretion would tend to stimulate it.

There are objections to this explanation. The concept of a sodium-losing factor does not seem physiological, and the existence of such a factor has never been demonstrated conclusively. Moreover, patients with virilising adrenal hyperplasia without an associated salt-loss (especially those who had had the salt-losing syndrome in their youth) should show a raised aldosterone excretion. Yet, according to the data of Blizzard et al. (1959), they do not always do so. Considering that a defect of hydroxylation at C_{21} is supposed to be the cause of virilising adrenal hyperplasia, it is rather surprising that any aldosterone can be produced at all. Different degrees of the enzymatic defect (Bongiovanni 1955) or a difference in distribution of the defect in the adrenal cortex might explain the exceptions cited above.

Alternatively one might develop another explanation. Under the influence of cortisone the changes in the excretion of 17-ketosteroids and of aldosterone seem to occur simultaneously, and this might suggest an identical mechanism. If, like the raised 17-ketosteroid excretion, the raised aldosterone excretion were due to a rise in the secretion of corticotrophin, cortisone would inhibit it in the same way. Here again one would have to invoke a different degree of defect in hydroxylation at C_{21} to explain why in some cases a high level of 17-ketosteroids and a low level of aldosterone are found in the urine.

There are many arguments against this explanation. The dependence of aldosterone secretion on corticotrophin is only very slight. It would not explain why exogenous corticotrophin may produce sodium diuresis in these patients and why the amounts of desoxycorticosterone needed to control the salt-loss patients are greater in untreated than in cortisone-treated patients.

More work will have to be done to decide this issue, but the inhibition of aldosterone excretion by cortisone will have to be taken into the account.

Summary

A raised level of aldosterone excretion was found in two patients with virilising adrenal hyperplasia. Cortisone reduced it to normal levels. The implications are discussed.

REFERENCES

Blizzard, R. M., Liddle, G. W., Migeon, C. J., Wilkins, L. (1959) *J. clin. Invest.* **38**, 1442.
Bongiovanni, A. M., Eberlein, W. K. (1955) *Pediatrics*, **16**, 628.
Crigler, J. F., Silverman, S. H., Wilkins, L. (1952) *ibid.* **10**, 397.
de Graeff, J., Moolenaar, A. J. (1957) *Ned. Tijdschr. Geneesk.* **101**, 1298.
Kassenaar, A. A. H., Huis in 't Veld, L. G., Siderius, P., Seldenrath, H. D., Querido, A. (1950) *Acta endocr.* **18**, 60.
Moolenaar, A. J. (1957) *ibid.* **25**, 161.
Prader, A., Spahr, A., Neher, R. (1955), *Schweiz. med. Wschr.* **85**, 1085.

DIET AND WEIGHT-REDUCTION IN THE OBESE

T. R. E. PILKINGTON
M.D. Lond., M.R.C.P.
SENIOR LECTURER

H. GAINSBOROUGH
M.A., M.D. Cantab., F.R.C.P.
CONSULTANT PHYSICIAN

V. M. ROSENOER
M.B., B.Sc. Lond., M.R.C.P.
FIRST ASSISTANT

M. CAREY
B.Sc.
CHIEF DIETITIAN

MEDICAL UNIT, ST. GEORGE'S HOSPITAL, LONDON, S.W.1

Kekwick and Pawan (1953, 1956) stated that, during short periods on isocaloric sub-maintenance diets, weight loss was greater when most of the calories were supplied by fat than when most were supplied by carbohydrate. Since they had not observed failure to absorb fat, or changes in basal metabolic rate, they suggested that this difference was due to a specific dynamic action of fat much larger than had previously been observed. Unfortunately, their findings have been used by others as a basis for slimming diets, an extrapolation which does not at present seem justified. We have therefore thought it important to repeat these experiments for longer periods.

Methods

Our study was carried out in the metabolic unit, where the patients were isolated from the general ward population. Full balance techniques were used, with total urine and fæcal collections, in six-day periods. Full details of the chemical balances will be reported elsewhere. The diets were constructed from the tables of McCance and Widdowson (1946), and each was analysed at least once for fat and nitrogen. The analyses agreed with the calculated values within 10%.

The patients, 7 women and 2 men, were all grossly obese by any standard. They were weighed at the same time each morning. Exercise was not controlled but was minimal. In a preliminary experiment on one other patient on an 800-calorie diet of varying composition, there was a linear fall in weight over a period of four months—from 103 to 78 kg. At this degree of obesity we felt quite happy to allow lengthy periods on each diet.

Experiment I (4 patients: 800 calories)

Patient 1. Male, aged 50. 96 kg.
Patient 2. Male, aged 52. 80 kg.
Patient 3. Female, aged 44. 106 kg.
Patient 4. Female, aged 59. 85 kg.

Patients 1 and 2 started on a mixed diet and then continued with patients 3 and 4 to take the following diets alternately for periods of eighteen days:

Protein (% *calories*)	*Fat* (% *calories*)	*Carbohydrate* (% *calories*)
13	9	78
15	62	23

Total water was constant for each patient at chosen level but differed in the two diets. Salt ad libitum.

Experiment II (2 patients: 1000 calories)

Patient 5. Female, aged 54. 94 kg.
Patient 6. Female, aged 39. 147 kg.

The diets were alternated every twenty-four days.

Protein (% *calories*)	*Fat* (% *calories*)	*Carbohydrate* (% *calories*)
17	8	75
17	70	13

Total water was constant for each patient at chosen level (1·6 litres, 1·8 litres.). Sodium was constant for each patient at chosen level (1·8 g., 2·3 g.).

Experiment III (3 patients: 1000 calories)

Patient 7. Female, aged 49. 111 kg.
Patient 8. Female, aged 28. 109 kg.
Patient 9. Female, aged 52. 127 kg.

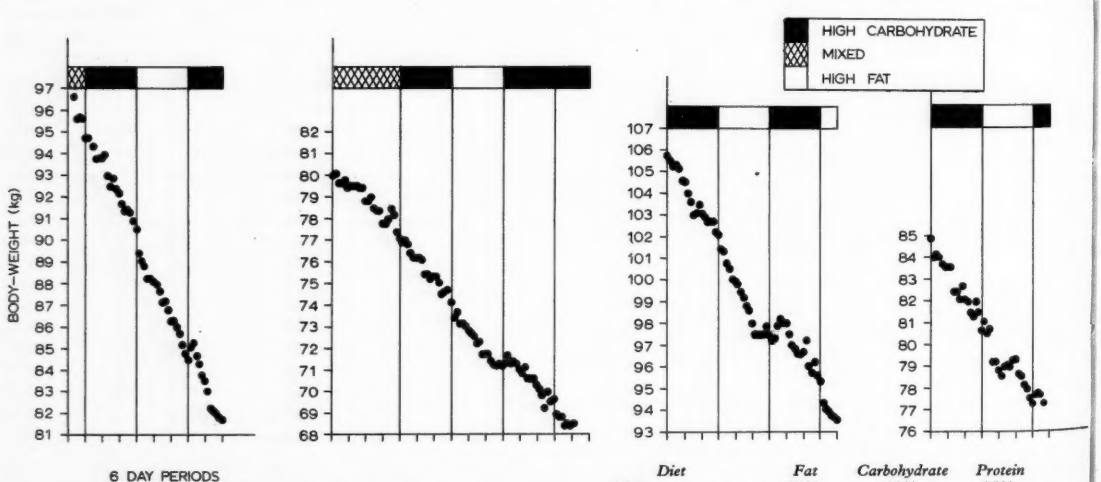
The following diets were alternated every twenty-four days (patient 9 started on a mixed diet):

Protein (% *calories*)	*Fat* (% *calories*)	*Carbohydrate* (% *calories*)
5	4	91
5	86	9

Total water was constant for each patient at chosen level (1·9 litres, 2·1 litres, 1·8 litres). Sodium was constant for each patient at chosen level (1·5 g., 2·5 g., 2·5 g.).

Results

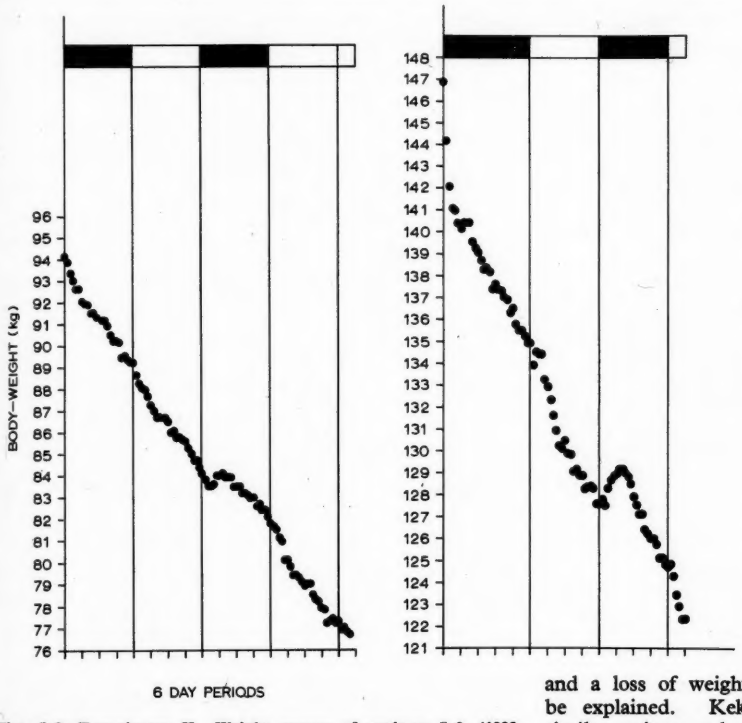
Our results are presented in graphic form (figs. 1–9, representing patients 1–9). When the curves are viewed as a whole the constancy of the weight loss is obvious, and the similarity of the results shows that the patients must have been very cooperative. There are regular deviations from the main line: weight is gained when the diet changes from high-fat to high-carbohydrate, and lost when the



Figs. 1-4—Experiment I. Weight curves of patients 1-4. (800 calories.)

Diet	*Fat*	*Carbohydrate*	*Protein*
Fat	62%	23%	15%
Carbohydrate ..	9%	78%	13%
Mixed	35%	35%	30%

Salt ad libitum. Total water was constant for each patient but varied with each diet.



Figs. 5-6—Experiment II. Weight curves of patients 5-6. (1000 calories.)

Diet	*Fat*	*Carbohydrate*	*Protein*
Fat	70%	13%	17%
Carbohydrate ..	8%	75%	17%

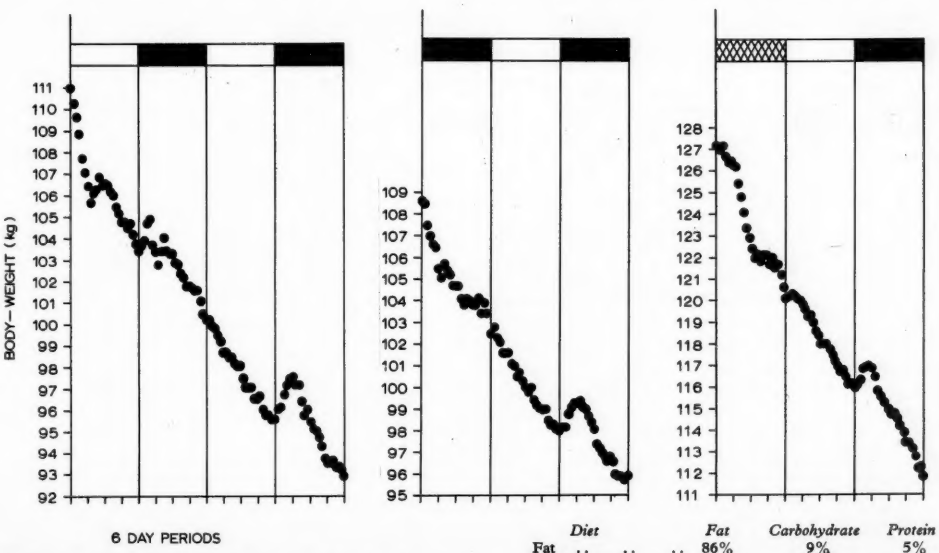
Total water and sodium were constant at chosen level.

change is in the reverse direction. These " swings " last up to ten days and may amount to 2·5 kg. For statistical analysis we therefore only used the part of the curve after the twelfth day on each diet, assuming this to represent a " steady state of weight loss". No significant difference was found in the rates of weight loss, whatever the diet. Throughout most experiments the patients were in negative nitrogen balance —more so when on a high-fat diet, when there was also a moderate degree of ketosis. The fæcal fat excretion was normal and constant.

The 3 patients on the 85%-fat diet complained of tiredness and nausea towards the end of each period. On the 91%-carbohydrate diet, they said that they felt invigorated but hungry. On the other diets opinions varied.

Discussion

From this study it may be concluded that, over the periods studied, isocaloric sub-maintenance diets are equally effective in weight reduction whatever their composition. The swings about the main weight curve—a gain in weight when high carbohydrate intake succeeds a high fat intake, and a loss of weight on the reverse change—have to be explained. Kekwick and Pawan (1956) showed similar swings and attributed them to changes in the metabolic requirements of their patients on different diets, but they produced no evidence of these changes. Anderson (1944) attributed them to the different salt contents of his diets, leading to water retention or loss. However, we found the changes—as did Kekwick and Pawan (1956)—even when the salt content of the diets was held constant. The swings can be explained largely by variations in the fluid balance which we have observed, but the amounts are not large enough to be detected



Figs. 7-9—Experiment III. Weight curves of patients 7-9. (1000 calories.)

Diet	*Fat*	*Carbohydrate*	*Protein*
Fat	86%	9%	5%
Carbohydrate ..	4%	91%	5%
Mixed	40%	35%	25%

Total water and sodium were constant at chosen level.

accurately by measurements of total body water. This is the explanation also given by Lyon and Dunlop (1932). Further studies are in progress.

Summary

On 800-calorie and 1000-calorie diets very obese patients lose weight steadily over periods of up to four months.

If the periods of study are long enough to achieve a " steady state " the rate of weight loss on a diet consisting mainly of fat does not differ significantly from the rate of weight loss on an isocaloric diet consisting mainly of carbohydrate.

When these diets are interchanged, deviations from the weight curve occur, lasting up to ten days. These can be accounted for mainly by changes in the fluid balance.

This work was supported by a research grant from the board of governors of St. George's Hospital. We are also grateful to Sister B. M. Jenner and her staff; to the dietitians, Miss F. M. Simmonds, Miss A. Pyper, and Miss V. S. Hankin, who supervised the study so meticulously; to Mr. W. H. Brough, who prepared our graphs; and lastly to all our patients, without whose cheerful cooperation the investigation could not have been made.

REFERENCES

Anderson, A. B. (1944) *Quart. J. Med.* **13**, 27.
Kekwick, A., Pawan, G. L. S. (1953) *Arch. Middx Hosp.* **3**, 139.
— — (1956) *Lancet*, ii, 155.
Lyon, D. M., Dunlop, D. M. (1932) *Quart. J. Med.* **1**, 331.
McCance, R. A., Widdowson, E. M. (1946) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 235.

Preliminary Communication

MALFORMATION SYNDROME IN MAN ASSOCIATED WITH TRIPLOIDY (69 CHROMOSOMES)

THE importance of chromosomal variations in human pathology has been firmly established in the past two years. Fifteen different types are known to us at present. Eight have been discovered here.[1–4] The aberrations include trisomy, monosomy, and translocations. The highest chromosome number was 49, interpreted [4] as a double trisomy with XXY. All these numerical variations represent unbalanced karyotypes, probably caused by non-disjunction during oogenesis or spermiogenesis.

Polyploidy has been known in plants and lower animals for a long time. In natural populations of vertebrates it is probably quite rare, but conclusive cases are known—e.g., among amphibia.[5] In mammals no conclusive post-term individuals have been found, but polyploid early embryos are known in rabbits and mice.[6]

The discovery of the first individual of the human species with triploid cells is of considerable interest from many viewpoints. It should, however, be remembered that this individual was found among a series of patients selected for chromosome studies. The condition with which the triploidy is associated may be accidental or peculiar to this particular individual. At this juncture and in this short note it can only be said that the findings have many important medical and genetical implications which we intend to consider fully in a later publication.

The patient is a boy born on Feb. 26, 1959, when his mother was 30 and his father 29 years old. Neither his parents (who were unrelated) nor his brother, born in 1957, showed clinical signs of disease or defect.

1. Böök, J. A. *Acta soc. med. Uppsala* (in the press).
2. Fraccaro, M., Kaijser, K., Lindsten, J. *Lancet*, April 2, 1960, p. 724.
3. Böök, J. A., et al. Unpublished.
4. Fraccaro, M., et al. Unpublished.
5. Böök, J. A. *Hereditas*, 1940, **26**, 107.
6. Beatty, R. A. Cambridge Monographs on Experimental Biology, 1957, no. 7.

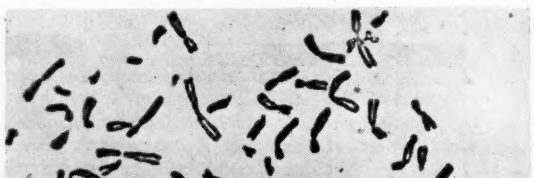


Fig. 1—Metaphase with 69 chromosomes.

The pregnancy and delivery (breech presentation) were normal. Although born at full term, at birth he weighed only 2190 g. Malformations were observed at birth. His subsequent development was retarded and there were occasional feeding difficulties.

The boy was brought to the pædiatric clinic at Örebro on Feb. 2, 1960, because of recurrent attacks of fever combined with disturbances of consciousness. On examination (Dr. Olof Brandberg) he was unable to raise his head when lying flat on his back. He showed some interest and played with toys but in general contact was deficient. He was small for his age (height 72 cm.). He had localised lipomatosis on the back of his hands, feet, and thighs. In contrast the lower legs were quite thin. His jaws were hypoplastic (micrognathia), and he had cutaneous as well as bony syndactyly of his hands and feet. The internal organs appeared normal. His genitalia were likewise normal with regard to his size and age. Both testes could be felt in the scrotum and had a normal consistence. The reflexes were normal; but a peculiar pattern of movements, including some ataxic features, was observed.

Radiographic examination.—In the skeleton 9 bone nuclei were found instead of the expected 16. No teeth had erupted, but germs were present. A pneumoencephalogram showed good filling of the ventricles with no displacement or deformity; but the basal cistern was much dilated, and large air spaces were observed bilaterally over the frontal convexity and parietally on the right side. The radiologist's diagnosis was porencephaly.

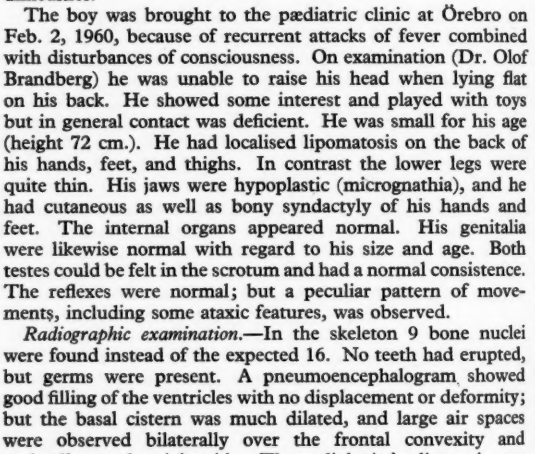


Fig. 2—Chromosomes in fig. 1 matched to show presence of three haploid sets: sex chromosomes interpreted as XXY.

Laboratory data.—Meinicke-Kahn test, dye test (Sabin-Feldman) test, and complement-fixation test for toxoplasma were all negative. Hæmoglobin 88%; red blood-cells 4,400,000 per c.mm.; white blood-cells 12,000 per c.mm.; erythrocyte-sedimentation rate 13 mm. in the first hour (Westergren).

Biopsy specimens were taken from skin. Chromosome studies were made according to our standard procedures [7] using the cell-culture technique. In the 11-day-old primary cultures which are the only ones analysed so far, practically all acceptable metaphases (>25) contained 69 chromosomes (fig. 1); occasional cells with lower or higher numbers were observed. The findings, exemplified in fig. 2, indicate the presence of three haploid sets—i.e., a chromosome complement of 3A+XXY.

For the preliminary clinical information we are obliged to Dr. Olof Brandberg, head of the division of Pædiatrics, Örebro Central Hospital.

J. A. Böök
M.D.
Berta Santesson
FIL. LIC.
Institute for Medical Genetics,
University of Uppsala, Sweden.

7. Böök, J. A., et al. *Acta pædiat., Stockh.* 1959, **48**, 453.

New Inventions

ANAL CANAL SUPPOSITORY

In conjunction with the instrument department and the pharmacy of the Middlesex Hospital, I have devised a simple suppository to reduce the painfulness of certain anal canal conditions. Made of suppository base in which is dissolved xylocaine 2% or similar local anæsthetic, the appliance is shaped rather like a chess pawn, with a spherical tip 1·1 cm. in diameter, and a rounded shaft 3 cm. long and 0·9 cm. in diameter, which widens out into a base 2 cm. in diameter. It is cast in a modified suppository mould, with braided silk down the centre to prevent breakage (fig. 1).

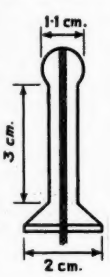


Fig. 1.

Fig. 2.

It is simple to use; it should be inserted into the anal canal so that the spherical tip lies above the anorectal ring and the base lies externally (fig. 2).

The main advantage of this suppository is that, while melting, it remains within the anal canal by virtue of its shape, thus delivering local anæsthetic in a suitable concentration throughout the anal canal. Other suppositories either slip out or slip above the anorectal ring into the ampulla of the rectum. Another advantage is that this suppository can be inserted without the anus being dilated by the finger because its diameter is smaller than that of the finger.

Trials in this hospital so far suggest that this suppository is extremely useful in painful fissure-in-ano, giving relief for several hours, and facilitating dilatation. It also relieves much of the pain if used before mechanical dilatation and before defæcation in the days following hæmorrhoidectomy. It seems to be more effective than systemic analgesics or local anæsthetic jellies.

A similar suppository could contain suitable substances—e.g., hydrocortisone, fungicides, or antibiotics—for other conditions of the anal canal.

A. B. J. Miller-Williams
M.B. Cantab.
Peace Memorial Hospital,
Watford, Herts

Reviews of Books

Delinquency and Parental Pathology

Robert G. Andry, ph.d., senior clinical psychologist, St. Thomas's Hospital, and lecturer in psychopathology, University of London. London: Methuen. 1960. Pp. 173. 30*s*.

The spectre of the incompetent or absent mother hangs over our child-guidance services. Counselling sessions between social workers and mothers of disturbed children are apt to be long and dynamic. Father is rarely called in, save as a witness to fact, and his eccentricities are often blamed upon his wife. We have not been alone in calling for [1] a resurrection of the father-image as a matter of importance in any child's upbringing, and Dr. Andry has done a service in comparing parental attitude and practice towards 80 thieving and 80 "control" 12–15-year-old lads from working-class London.

Maternal identification seemed commoner among delinquents, and environmental communication with both parents, especially father, was poorer. When in trouble delinquents consulted their parents less readily than the controls, and while delinquents usually turned to mother, controls turned to father, or to both. Mothers of delinquents, however, were more lenient and fathers more emotional in their reactions. Breast-feeding lasting over 9 months was significantly more common among controls. Delinquents showed the usual preponderance of aggressiveness, resentment, and non-constructive social activity. Separation from either or both parents seemed little different in the 2 groups, though, if anything, the fathers of delinquents were absent more often (allegedly due to work).

This study is subject to all the objections that surround retrospective surveys and certainly does not eliminate maternal deprivation as a crucial factor. What a delinquent tells the interviewer in a remand home about his father, &c., may be coloured by his cruel fate and by negative transferences towards all the "bad fathers" he has lately encountered. A questionnaire-interview, however well designed, tells us little about the *quality* of a relationship. Though delinquents felt themselves loved, particularly by mother, whereas controls nominated both parents, this need not imply (as Dr. Andry claims) a causal defect in the delinquent's relationship with father. We know far too little from his meagre data of what the mother love means in each case. Nor was there any test-retest, split-half, &c., validation of the methods used in gathering the data, though on some matters the views of parents and child correlated quite well. Moreover, exclusion of children with neurotic traits and those from broken homes (we are not told how many were thus rejected) and the smallness of the final sample do not help towards an "over-all" view of delinquency. A rather more serious criticism is that all subjects and parents were interviewed in full knowledge of their "delinquent" or "control" status, so that an interviewer's particular bias could have seriously affected the responses. The more valid work of the McCords [2] on Massachusetts families suggests that Dr. Andry may be overstating his case.

Pending the larger longitudinal study that must one day be done "under the roof", however, this lucid work is very valuable in helping tentatively to put Father back into the picture, and in emphasising the bonds of love that must exist between a boy and his parent, of whichever sex, if healthy development is to take place.

Biochemistry of Blood in Health and Disease

I. Newton Kugelmass, m.d., ph.d., sc.d., consultant, Departments of Health and Hospitals, New York. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 543. 126*s*.

The object of this book is "to present the newer knowledge of human blood in health and disease in the light of chemical research, clinical experience and medical necessity". It is arranged in three parts: blood in the transport system, blood as the regulating system, and blood as the defence system. The last part rather oddly contains much that is ordinarily

1. *Lancet*, 1958, ii, 625.
2. McCord, W., McCord, J., Origins of Crime, New York, 1959.

classed as "hæmatology", and includes discussion of such subjects as pigment disorders of heme and the hereditary hæmoglobinopathies.

The chapters are packed with solid information, but often collected in an uncritical way. For example, a table of distribution of protein components in blood lists, for plasma alone, 11 enzymes, 15 antibodies, 4 coagulants, 3 metal-proteins, and 8 lipid complexes, and another table lists 11 causes of hypophosphatæmia and 16 of hyperphosphatæmia. There are many informative diagrams reproduced from the work of experts—e.g., Hartmann's figure showing the primary areas of disturbance of carbohydrate metabolism; Granick's on the mechanism for iron absorption into a cell of the intestinal mucosa, movement of the iron within the cell, and its delivery into the blood; and one of Owren's most complicated figures on the production and prevention of blood coagulation. Then there are many comprehensive tables of quantitative information—for example, the composition and properties of plasma lipoprotein, figures for the acid-base levels of blood at different ages, the blood-copper in 13 diseases, and figures for 60 different chemical components of the erythrocyte (plus 30 components just listed without any figure). The largest table of all is in the appendix, and it gives figures for the normal range of concentrations of over 200 "blood components", including such things as aldolase, diphosphoglycerate P, indican, norepinephrine, pseudoglobulins I and II, and water. All this material is listed in an indiscriminating way, but the source is nearly always quoted and this gives some guide to its reliability.

Like most compendiums, the book is not meant to be read, but it is a remarkable reference volume to information usually scattered about many monographs. For that reason it is well worth having on the library shelf among the biochemical reference books.

Stepping Stones to Labour Ward Diagnosis

R. H. J. HAMLIN, M.B., M.R.C.O.G., formerly medical superintendent, Women's Hospital, Crown Street, Sydney. Adelaide: Rigby. 1959. Pp. 160. 10*s*. 6*d*.

IN this small book Dr. Hamlin is concerned with the early diagnosis of abnormalities in the first and second stages of labour. He has set down, for students, residents, and midwives, the principles which have guided him in his own work in the labour ward. His views on the diagnosis and significance of cephalo-pelvic disproportion and of abnormal presentation of the fœtus in labour are supported by diagrams, case-histories, and references to the literature. His aims are clear, but the choice of material and the emphasis given to various sections will surprise some readers. A great deal is made, for example, of asynclatism, but nothing is said about the diagnosis of breech, brow, or shoulder presentation or of the factors which predispose to these abnormalities. Much of the book deals with difficult labour, associated with minor degrees of contracted pelvis, but no reference is made to the fundamental research carried out in Aberdeen since 1947 into the relationship between stature, pelvic shape, and difficult labour. Inevitably in a book of this size the teaching tends to be dogmatic—not necessarily a bad feature.

Textbook of Toxicology

KENNETH P. DUBOIS, M.SC., PH.D., professor of pharmacology, and director, United States Air Force Radiation Laboratory, University of Chicago; E. M. K. GEILING, PH.D., M.D., Frank P. Hixon distinguished service professor emeritus of pharmacology, University of Chicago. London and New York: Oxford University Press. 1959. Pp. 302. 52*s*.

THIS book deals with the pharmacological, clinical, and therapeutic aspects of a number of poisons, including most of the familiar ones and many of the less well-known though contemporary poisons to be found in the home often in a seemingly harmless guise. The chapter on household poisons is a miscellany of toxic substances from drugs to cosmetics and crayons. Other chapters deal with the poisonous properties of airborne substances (fairly detailed attention being given to toxic dusts), and of metals, corrosives, pesticides, solvents, and other compounds. One section is devoted to radiation hazards. It is surprising that, among such a number of toxins of which many are not encountered in ordinary medical practice, there is scarcely a mention of aspirin or barbiturates, and neither is included in the list of contents or the index.

An account of the historical development of toxicology is an admirable opening chapter of this easily read book, but the details of the medicolegal aspects of toxicology apply to American practice and thus have a limited value outside that country. The section on analysis deals with general principles rather than practical instruction, and it may mislead when listing the specimens routinely required for toxicological analysis, for there are several important omissions (blood, for one), and not all forensic specialists would accept the wisdom of preserving organs for analysis in formalin or ethyl alcohol.

The Royal Edinburgh Hospital for Sick Children 1860-1960

DOUGLAS GUTHRIE, M.D., F.R.C.S.E. Edinburgh: E. & S. Livingstone. 1960. Pp. 76. 17*s*. 6*d*.

THIS volume worthily tells the story of the hospital known familiarly and affectionately as "Sick Kids" from its modest beginning a hundred years ago to the present day when it has become one of the leading pædiatric hospitals in the world. The author, who has had assistance from seven distinguished contributors, one a Sister and another the Secretary, has illustrated his book lavishly, and the endpaper maps of Edinburgh then and now make the story easy to follow. Great names fill the pages and there are some excellent biographies.

Prof. R. W. B. Ellis contributes a challenging chapter on recent developments. These have been accomplished only by using endowment funds. And there is this warning: "The Hospital cannot hope to retain its proper status—either in teaching, research or service to the community—unless Regional Boards recognise and fulfil their special obligations to the teaching hospitals as spearheads of progress requiring more than the basic necessities for routine hospital service . . . In planning for the future full recognition must be given to the part which the hospital can and should play in improving child health throughout the world." There is a lively and most interesting chapter on Matrons and Nurses. There were difficulties in the early years. "A wage of £14 a year, the obligation to clean and scrub the wards in addition to extensive nursing duties, beer only when cold beef was served for dinner" made it hard to enlist suitable nurses. Anyone connected with or interested in the hospital will treasure this book.

Recent Advances in Surgery (5th ed. London: J. & A. Churchill. 1960. Pp. 500. 60*s*.).—In keeping with the notable advances in surgery in the past five years the whole book has been rewritten, to survey those branches in which important progress has been made, and also to consider what recent innovations may have to offer and review "those subjects of which during recent years it has been possible to obtain a clearer picture of what may be expected from well-tried techniques if properly applied . . .". In these objects the editor, Mr. Selwyn Taylor, with the help of 28 contributors, has been notably successful, and he deserves warm congratulations for this outstanding addition to British surgical literature. Most of the chapters are concerned with individual conditions or organs, such as hydronephrosis or the parotid gland, but there are more general chapters, such as those on the body fluids and tissue transplantation, which reflect the increasing scope of surgical thought. The six chapters dealing with the surgery of the heart and peripheral vascular system are outstanding. The book is excellently produced, with an adequate index and a useful list of selected references at the end of each chapter.

THE LANCET

LONDON 16 APRIL 1960

The Medical Service Committees

A PATIENT who has a complaint against a practitioner under the National Health Service has three possible remedies. The patient (or certain specified persons on his behalf) may complain to the appropriate service committee on the ground that there has been a breach of the terms of service—which include, in the case of doctors, requirements as to "proper and necessary treatment". If the complaint is substantiated there will be a report to the executive council, which may recommend "disciplinary" action against the practitioner; but the patient will not obtain redress in the form of damages. If, however, the complaint is of professional negligence, the patient can sue for damages in the courts of law. And in certain cases he may be justified in complaining to the General Medical Council, though here again he will not obtain any redress for himself.

Is the system of hearing complaints by a service committee fair and reasonable? In their evidence to the Committee on Administrative Tribunals and Enquiries (the Franks Committee) [1] the Ministry of Health and the British Medical Association both defended it on the ground that it has worked satisfactorily and that it has the general consent of the professions concerned. Other witnesses, however, were strongly critical, principally on the ground that the numerous stages involve delay and—significantly—that the scales are weighted in favour of the practitioner. Nevertheless, some practitioners feel that the system is indefensible. In a letter which we publish in this issue Dr. WHEATLEY describes it as "a humiliating and time-wasting procedure" in which the scales are weighted heavily against the doctor from the start, and he would apparently limit the right of complaint to the ordinary remedies of action in the courts or before the General Medical Council.

The difficulty here is that the legal relation between an N.H.S. practitioner and his patient is not the same as that between other professional men and their clients. In the latter case there is a contract between the professional and his client, and a dissatisfied client can withhold his fees, leaving the other party to take the matter to the courts if he wishes. The N.H.S. practitioner's fees are paid by the State and his contract is with the executive council—not with the patient. If there is a complaint against a practitioner, it ought to be reported and investigated on behalf of the executive council. Indeed, as the Franks Committee pointed out, the whole system is intended to uphold the efficiency of the health service. "The ultimate decision which can arise is whether a practitioner should be retained in the National Health Service or not, and the decision here must turn upon his general professional skill and behaviour as indicated by the evidence in one or more individual cases brought to the notice of the deciding authority." That is hardly the kind of decision which should be left to the courts.

There may well be scope, however, for improving the system. Some regard it as a defect that neither the practitioner nor the patient is entitled to be represented by counsel or solicitor at the hearing before the service committee, although legal representation is permitted at hearings on appeal to the Minister or the N.H.S. tribunal. Some of the issues involved are well reviewed in the Franks Committee report:

> "The importance which we attach to the proper finding of the facts at the first stage would seem in itself to be sufficient justification for introducing a right to legal representation. It can also be said that the present ban of legal representation operates to the advantage of practitioners . . . since practitioners are often represented before Service Committees by experienced representatives of their professional organisations. On the other hand it can be argued that the removal of the ban would also operate to the advantage of practitioners, since they and their representative organisations have greater resources and more at stake than the individual complainant and would therefore more often exercise the right to legal representation. Moreover, a complainant may be said to be acting to some extent in the general public interest, and it is arguable that he should not in so doing have to incur legal expenses."

These considerations led the Franks Committee to recommend that complainants should be assisted from official sources. At present there seems little likelihood that this will be done, and it might therefore be better to grant a straightforward right of legal representation to those who care to exercise it.

Some insist that further issues are at stake. In a discussion by the Middlesex Executive Council, Dr. R. B. L. RIDGE described how, in a High Court case in which he had been involved, counsel had torn his opponent's case into pieces: "I came to the conclusion I would never agree to any patient of mine, no matter what sort of charge he might make against me at a service committee, to suffer such a soul destroying attack at the hands of counsel".[2] Sometimes, of course, discovering the truth must involve a searching cross-examination in which the evidence of a witness may be torn to pieces. But this does not necessarily involve bullying a witness; and if counsel occasionally goes over the borderline of what is reasonable or legitimate, the judge or opposing counsel can always intervene. Provided the chairman exercises proper control, there is no reason why anyone should suffer from the presence of lawyers at hearings before a service committee; and the quality of the hearing might well be improved.

1. Cmnd. 218. See *Lancet*, 1957, ii, 225.

2. *Times*, March 17, 1960.

Commentary on the Cardia

INTEREST in œsophageal sphincter mechanism[1] continues, and evidence is accumulating that an intrinsic mechanism not only is present but is effective rather than vestigial. INGRAM et al.[2] have undertaken experiments to prove the efficacy in dogs of a sphincter vis-à-vis external mechanisms. After transection of the œsophagus 3 cm. above its termination and conversion of the distal portion into a blind pouch replaced into the thorax through the diaphragmatic aponeurosis, no œsophagitis developed in the pouch transplanted with the sphincter intact (care was taken not to damage the vagus); but inflammation and ulceration developed in the proximal œsophagus anastomosed to the stomach through the normal hiatus, and thus dependent on external mechanisms only for its protection against reflux. The œsophagitis thus induced subsided once the normal anatomy was restored by bringing the lower end, and thus the internal sphincter, into circuit again. When the lower segment was retained as a blind pouch but invaginated into the stomach, and so bathed in gastric juice while robbed of sphincteric protection, ulceration again developed.

Here is incontrovertible evidence of a functioning sphincter in a pronograde animal. A bat hanging upside down presumably has even greater need; and that this need is provided for has been demonstrated by BOTHA,[3] who dissected a wide number of species from a dogfish to a tortoise and demonstrated a considerable variation in situation, size, and type according to species. BOTHA found no sphincter in the pronograde dog, cat, ferret, and monkey. But the presence or absence of a sphincter *mechanism* cannot be established on the anatomical findings alone: the experiments of INGRAM et al. revealed an intrinsic sphincter mechanism in the dog, in which BOTHA's dissections failed to reveal any intrinsic sphincter. The smooth circular muscle-fibres at the lower end, whether or not in greater bulk than elsewhere in the œsophagus, presumably act as a sphincter in relation to the fibres at a higher level. Perhaps man, in the orthograde position, hardly needs a strong sphincter; but, as recent investigations have shown,[4] an internal sphincter mechanism cannot be discounted because there is little to be seen in the way of a sphincter. Dr. GOLDBERG, whose report we published last month,[5] has carried understanding a little further by the neat and simple expedient of radiographic assessment during operative repair. By barium studies he showed in patients with hiatal hernia that, though clearance of the hiatus and removal of the hiatal hernial sac does not stop reflux into the œsophagus, approximation of fundus to œsophagus by a few stitches does, since this distributes the gastric pressure over the fundal wall; with a more obtuse cardio-œsophageal angle the sphincter receives and is overcome by the full pressure of a force directed upwards into the fundus, which in this position acts as an aditus or funnel directing the pressure against the sphincter instead of taking the strain from it. ZDANSKY[6] has stressed loss of fixation of the gastric fundus in the subphrenic space as an important element in reflux; this displacement leads to alteration of the cardio-œsophageal angle.[7] The value of GOLDBERG's observations lies in the radiological proof that simple restoration of acute angulation is effective in man. ATKINSON,[8] in a study of 18 patients who had undergone cardiomyotomy, showed that impairment of the sphincter mechanism was greater in those with than in those without postoperative reflux; but in 3, even though no sphincter mechanism could be demonstrated, symptoms of reflux did not develop—perhaps because the angle remained acute enough for the fundus to retain its function as a shock-absorber.

1. See *Lancet*, 1958, ii, 357.
2. Ingram, P. R., Respess, J. C., Muller, W. H. *Surg. Gynec. Obstet.* 1959, **109**, 659.
3. Botha, G. S. M. *Acta anat.* 1958, **34**, 52; *Ann. R. Coll. Surg. Engl.* 1959, **25**, 91.
4. Botha, G. S. M., Astley, R., Carré, I. J. *Lancet*, 1957, i, 659. Atkinson, M., Edwards, D. A. W., Honour, A. J., Rowlands, E. N. *ibid.* 1957, ii, 918, 1138.
5. Goldberg, H. M. *ibid.* March 19, 1960, p. 613.
6. Zdansky, E. *German med. Monthly*, 1959, **4**, 331.
7. Collis, J. L., Kelly, T. D., Wiley, A. M. *Thorax*, 1954, **9**, 195. Marchand, P. *Brit. J. Surg.* 1955, **42**, 504.
8. Atkinson, M. *Thorax*, 1959, **14**, 125.
9. *Birmingham Post*, Feb. 13, 1960; see *Lancet*, Feb. 20, 1960, p. 446.
10. *Times*, Feb. 8, 1960.
11. *ibid.* Feb. 3, 1960.
12. Casualties of the Welfare State. 1960. Pp. 32. (2*s.* 8*d.*, post free, from the Fabian Society, 11, Dartmouth Street, London, S.W.1.)

The Right Help in the Right Place

OUR social services have developed rapidly since the war, but justifiable pride in them must not turn into complacency. For some people still lack adequate and timely support, as may be seen from the following reports from the daily press:

> An epileptic, who was expecting her third child in three months' time, appeared before a magistrate's bench on a charge of stealing. She had to be repeatedly remanded to prison because she had nowhere to go. Four epileptic colonies refused to take her because she was pregnant, while a "mother-and-baby" home refused to take her because she was an epileptic.[9]

> Four sisters, the eldest aged 6, died in a fire in their home which was a converted bus on an unlicensed caravan site. There was no fire-extinguisher on the site and only one standpipe for water. Their parents, who had a family of six children, had been evicted from a council house.[10]

> A family of ten, including eight children aged between 11 years and 18 months, were found living in a disused chalet, 10 ft. by 8 ft. The mother was expecting another child. There were neither blankets nor heating and the household goods consisted of two beds, two mattresses, and a hurricane lamp.[11]

These families all came to public notice when a crisis in their lives brought the parents before magistrates or coroner. Despite our social services, each had already been living for some time in unsuitable or even dangerous conditions, and the reader is left with the uneasy feeling that other needy pre-crisis families are also struggling without effective help.

This unhappy hypothesis is confirmed by Mrs. AUDREY HARVEY's experience in a citizens' advice bureau in one of the poorest districts in London, where for five years she has been helping working-class people with their difficulties and questions. In a Fabian tract[12] she discusses how and where the social services still fail the sizeable minority who have less money, education, living space, opportunity, and status than the rest of us. In

another Fabian tract[13] Prof. R. M. TITMUSS has reiterated his view that the better-off third of the population enjoy fiscal and occupational benefits at the expense of the welfare services which could offer real support to those who are "living precariously close to the margin of poverty". Mrs. HARVEY agrees with this: indeed in her view it is chiefly the middle classes who have benefited from some recent developments of the social services, notably the National Health Service. In unfair contrast, the poor carry a burden of indirect taxation which for them is relatively heavier than for the better-off. Though widows, old people, and the sick are eligible for benefits, these are modest and the regulations hedging extra earnings and National Assistance are, in Mrs. HARVEY's view, irksome and often harsh.

The most urgent basic need of the poor, she thinks, is cheap housing. Yet local-authority building fell from 200,000 dwellings in 1954 to 113,000 in 1958 (though over the same years private building expanded). The "general need" housing subsidy, abolished in 1956, has never been restored, and she says that we spend a lower proportion of our income on housing than all but three of fifteen other European countries. It is a commonplace that the home is the centre of family life, and for a family of wavering stability it may make all the difference between independence and reluctant reliance on the social services. Each of the three examples we cited above had failed to find reasonable accommodation, and a section of Mrs. HARVEY's tract describes in detail the misfortunes of a family which almost disintegrated, largely from lack of a home of their own. Though they were given a great deal of expensive help from various social services, no authority seemed able to provide them with the house or flat which at much less cost would have set them on their feet again. "It is one of the salient anomalies of the Welfare State", she writes, "that despite its insistence on 'the importance of the family', far more services are provided for efficiently sweeping under the carpet the remains of a family after it has disintegrated than for preventing this disaster. Nor is it generally recognised that what is needed to prevent this is far less often solemn amateur psychiatry than helpful information and advice and, sometimes—in an emergency—just plain cash as a loan". This last sentence expresses Mrs. HARVEY's dissatisfaction with the manners as well as the matter of the Welfare State. In her work at a citizens' advice bureau in a poor district, she has perhaps tended to meet an undue proportion of those who have found its administration bewildering and its help grudging. Standing outside the official specialist services as she does, she has come to regard the professional social worker with some reserve. Though she recognises many notable exceptions, she finds among them a "terrifying tendency to blame unfortunate people for their misfortunes" and to expect of them standards of conformity and virtue "stern beyond belief". To those who see the work of the social services as a whole such criticism may itself seem unduly stern; but at a time when the Younghusband report has set us thinking about the organisation of the social services, her plea for a reconsideration of their purpose and deployment should not be neglected.

13. The Irresponsible Society. 1960. Pp. 20. (2s. 8d., post free, from the Fabian Society.)

Annotations

APPEAL FROM GREAT ORMOND STREET

THE Institute of Child Health, which was formed in 1946 and is associated with the world-famous Hospital for Sick Children in Great Ormond Street, London, has established itself not only as a national but also as an international centre. Most would agree that such a Mecca within each specialty is a necessity—for teaching post-graduates at all levels, for coordinating the study of special problems, and, above all, for research. And in the 1960s even Mecca must be up to date and look to the future.

The Institute has now reached the point where its resources are exhausted and it can neither accommodate all its would-be students nor properly fulfil its research projects. Those who study there can see all types of disease, and, for comparison, the relatively healthy children who attend the Province of Natal Welfare Centre. But the amenities for students are meagre, and the laboratory facilities are badly overcrowded. Such a situation must obviously be remedied quickly at a time when progress in medicine lies so largely in the laboratory. This is perhaps particularly true of pædiatrics, and of advances in the treatment of the sick newborn baby.

Because of the Institute's insufficient buildings and the growing demands made on it as a Commonwealth centre, a new and larger building has become a matter of urgency. A site is available, and plans are already drawn up; but though these include only provisions for the foreseeable future the estimated cost will be £400,000. As part of the British Postgraduate Medical Federation, the Institute would normally look to the University of London for funds from the allocation made by the University Grants Committee. But at present the universities are giving priority to expansion in technology and pure science, and the necessary money is unlikely to be given to the Institute quickly. Accordingly it has launched its own building appeal, in the hope that those who have benefited from the work of "Great Ormond Street", either directly or indirectly, and who believe that its future should match its past, will give all the support they can.

Donations may be sent to Sir Hugh Beaver at the Appeal Office, Institute of Child Health, Great Ormond Street, London, W.C.1.

PREVENTION OF SERUM HEPATITIS

SERUM hepatitis is potentially fatal, and every effort must be made to screen donor blood for the hepatitis virus. In the absence of specific means of identifying the agent or its antibodies, present screening methods are necessarily crude. Donors with a previous history of jaundice are unacceptable, but this does not exclude the significant number carrying the virus from a latent or anicteric form of the disease. In order to detect this group of hepatitis carriers, donor blood has been subjected to a battery of liver-function tests, but none has proved effective.[1 2]

1. Rosenberg, J. *N.Y. St. J. Med.* 1957, **57**, 2522.
2. Capps, R. B., Stokes, J., Jr. *J. Amer. med. Ass.* 1952, **149**, 557.

Since serum-glutamic-oxalacetic-transaminase (S.G.O.T.) activity was introduced as a sensitive index of hepatocellular necrosis,[3] this has naturally been studied as a possible screening-test to eliminate carriers of hepatitis virus. All donor bloods received in the blood-bank of the Memorial Center, New York, in 1956 were examined for S.G.O.T. activity.[4] The blood was infused before the results of these determinations were known; but from a subsequent follow-up the incidence of hepatitis in recipients was related to the S.G.O.T. activity of the blood they had received. Of 1371 adequately followed-up recipients, 603 patients received normal blood and 768 received blood with raised S.G.O.T. activity. Of the 1371 recipients, 39 developed hepatitis. The incidence of serum hepatitis was 1·5% among recipients of blood with normal S.G.O.T. activity, but 5·5% among those who received blood with S.G.O.T. values above 100 units. Since the differences were statistically significant it appeared that S.G.O.T. determinations would help in excluding hepatitis carriers among prospective blood-donors.

In order to arrive at these figures, it had been necessary to determine the S.G.O.T. activity of over 13,000 donor bloods, for many unpredictable variables marred the follow-up and final analysis. Nevertheless, these results, together with similar studies from other centres, should help to determine whether S.G.O.T. activity should be accepted as a standard screening measure in blood-banks in order to reduce the incidence of post-transfusion serum hepatitis.

DESENSITISATION IN HAY-FEVER

WHEN hay-fever is caused by grass pollen, desensitisation is ideally carried out with extracts of the particular pollen responsible for the trouble. But identifying the culprit is tedious; and as most English grass pollens are antigenically similar, some workers consider it enough to use extracts of random pollens.[5–8] Others believe that this practice is more convenient than effective,[9 10] and Feinberg [11] now reports the results of investigations which support this view.

Feinberg studied the antigenic relationships between the pollens of 11 common English grasses by refined immuno-diffusion techniques in agar-gel plates. He found that, although the so-called "common" antigen of one pollen would react with the antiserum of a different pollen, it did not react completely; each pollen had one or more specific antigens. Thus, while desensitisation with a heterospecific pollen could be expected to produce blocking antibodies to related antigens in the causal pollen and might give some relief, it would not produce the full complement of antibodies and so might fail to give complete relief.

If symptoms are the result of sensitisation to an antigen specific to the causal pollen, desensitisation with a heterospecific pollen will, of course, fail to give any relief at all. When sensitivity to grass pollen is suspected, skin testing with individual pollens should indicate the causal one, for, as only this will contain antigens corresponding to all the antibodies present, it should produce the most intense reaction; and Feinberg maintains that identification in this way of the pollen actually responsible for the trouble is an essential preliminary to rational therapy.

Clinical investigation of this matter is obviously desirable, for desensitisation treatment is so tedious that it would be a pity to employ any method but the best.

SUBDURAL HYGROMA

SUBDURAL effusions of clear fluid containing no blood were formerly regarded as of the same nature as liquid hæmatomas and were thought to be usually traumatic. Admixture of cerebrospinal fluid was ascribed to a tear in the arachnoid [1]; and the occasional demonstration of a communication by pneumoencephalography, and the frequency of signs of meningeal irritation, were held to support this hypothesis. Recent work has rendered this view untenable and has even cast doubt on whether such cases are ever traumatic in the sense that was originally meant. It was realised that such effusions might occur not only in meningitis [2] but also in other diseases not obviously accompanied by intracranial changes,[3–5] such as respiratory or intestinal infection or simple malnutrition. Suckling and Wittmann [6] have reported nine cases of coloured children in whom subdural effusion complicated respiratory infections such as tracheobronchitis and pneumonia. They conclude that, although hæmorrhage is not certainly an essential precursor, it is difficult to understand how else the exudation is caused.

The dural membrane has a capillary bed and is therefore capable of exudation in its own right. The arachnoid strictly has no capillary bed, though the pial vessels can exude blood or protein under pathological conditions, and pia is not easily distinguished from arachnoid at every site. Suckling and Wittmann report that in all their cases yellow fluid was obtained at the first tap, and that in the majority the fluid contained no obvious blood. No case of subdural effusion in whooping-cough has come to light, so the stress of coughing is unlikely to be a crucial factor. A positive Wassermann reaction is rare, while the sagittal sinus, whenever it has been investigated, has been patent. It has been objected that, if the effusion is aspirated first, the needle may have caused any tear revealed by subsequent pneumoencephalography; while pneumoencephalography may in turn lead to a subdural effusion.[7] Certainly, if a brain cannula is passed into an atrophic cerebral hemisphere, the arachnoid is breached; and this may be followed by a typical yellow, proteinous "effusion" in the subdural space. The factors here are a brain too small for the skull and a hole in the arachnoid membrane.

Fresh light is thrown on the mystery by the investigations of Hill et al.[8] into the levels of different proteins in cerebrospinal fluid. They conclude that these consist of a mixture of two distinct groups: one, characteristic of ventricular fluid, contains prealbumin, and probably results from some active process in tissue of the central nervous system; the other accumulates in the subarachnoid space on the basis of physicochemical properties

3. Wroblewski, F., La Due, J. S. *J. Lab. clin. Med.* 1955, **46**, 831. See *Lancet*, 1958, ii, 1318.
4. Bang, N. U., Ruegseggar, P., Ley, A. B., La Due, J. S. *J. Amer. med. Ass.* 1959, **171**, 2303.
5. Vaughan, W. T., Black, J. H. Practice of Allergy; pp. 543, 655, 690. London, 1954.
6. Frankland, A. W. *Int. Arch. Allergy*, 1955, **6**, 45.
7. Wodehouse, R. P. *ibid.* p. 65.
8. Grubb, G. D., Vaughan, W. T. *J. Allergy*, 1938, **9**, 211.
9. Feinberg, S. M. Allergy in Practice; pp. 58, 589. Chicago, 1946.
10. Sternberg, L. *J. Allergy*, 1952, **23**, 163.
11. Feinberg, J. G. *Int. Arch. Allergy*, 1960, **16**, 1.

1. Munro, D. *New Engl. J. Med.* 1942, **227**, 87.
2. McKay, R. J., Morisette, R. A., Ingraham, F. D., Matson, D. D. *ibid.* 1950, **242**, 20.
3. Guthkelch, A. N. *Brit. med. J.* 1953, i, 233.
4. Williams, J. M., Stevens, H. *Ann. Surg.* 1954, **139**, 287.
5. Herzberger, E., Rotem, Y., Braham, J. *Arch. Dis. Childh.* 1956, **31**, 44.
6. Suckling, P. V., Wittmann, W. *S. Afr. med. J.* 1959, **33**, 1057.
7. Smith, H. V., Crothers, B. *Pediatrics*, 1950, **5**, 375.
8. Hill, N. C., Goldstein, N. P., McKenzie, B. F., McGuckin, W. F., Svein, H. J. *Brain*, 1959, **82**, 581.

such as molecular weight and a gradient between the concentration in serum and in cerebrospinal fluid. The proteins in the fluid from clear subdural effusion (hygroma) contain the component characteristic of cerebrospinal fluid—prealbumin—whereas those from subdural hæmatoma do not. This indicates that the proteins of a hygroma are derived from cerebrospinal fluid. The fact that they are concentrated suggests that, whereas the proteins cannot be absorbed from the subdural space, water can. Only two such cases have been investigated, and it is not established that all subdural hygromas are of the same nature; but already it is clear that some, if not all, examples of subdural hygroma constitute a separate disease from subdural hæmatoma, though both may share one predisposing factor—namely, a tendency for the brain to fall away from the skull by reason of discrepancy in size. In hygroma this factor is particularly evident in children: in subdural hæmatoma it is more prominent at the other extreme of age.

In all the cases described by Suckling and Wittmann the condition cleared up with repeated aspiration. In view of the recent discoveries, stripping of the inner membrane is unlikely to be of much value in treatment.

GROWING UP IN NEWCASTLE UPON TYNE

AFTER the late war Sir James Spence inaugurated a new type of sociomedical investigation in child health with the object of examining many unsolved problems. Accordingly, a longitudinal study of the health and illnesses of all children born in Newcastle upon Tyne in the months of May and June, 1947, was launched, with the intention of pursuing it up to school-leaving age at 15 years. The number of infants enrolled was 1142, but the study embraced many times this number, for it inevitably became concerned with the families of all of them, since the child had always to be considered in his family context. Hence the investigation became generally known as the Thousand Family Survey. The success of such a project depends very largely on the cooperation and goodwill of all concerned, and the maintenance of these fine qualities by the parents, the family doctors, the staff of the city health department, and the staff of the university department of child health is clearly demonstrated by the continued participation of all but 7 of the original families still living in the area.

The account [1] of the investigation covering the first year of life aroused much interest, for it oriented the infant " within the family " and viewed various aspects of infancy from a new angle. Further unfolding of this fascinating continuing study of childhood has been eagerly awaited, and the second volume,[2] which has just appeared, covering the first five years of life, will be widely welcomed. The first part is concerned with the varying fortunes of the families during the five years, set against the social and economic background of Newcastle; and the second measures the child's environment in terms of housing, family, and medical care. The third part contains detailed accounts of illness and is arranged to show how diseases fall into new and more relevant groups when viewed in the family context. Part 4 is an estimate of the incidence of illness and defects in pre-school children in Newcastle based on the facts of the survey, and concludes with suggestions for further improvement in the health and wellbeing of children.

There was an average of 10 significant episodes of illness, excluding minor colds, minor skin sepsis, and herpes labialis, in each child in the first five years, 80% being infective illness and 20% non-infective. Respiratory infections including whooping-cough accounted for nearly two-thirds of the infective illnesses, followed by acute infectious fevers (15%) and alimentary infections (11%), these three together accounting for 87% of infective illnesses. Staphylococcal infections occurred in 5%, and 3% had acute infections of unknown origin. Nearly all the fatal infections were in the first year, as were nearly all the other serious infections apart from pneumonia. Nearly half of the 20% of illnesses which were non-infective were accidents, but few of these happened in the first year before the attainment of mobility. Developmental conditions, such as speech defects and non-infective skin rashes, accounted for most of the remainder.

The environment of the survey children was considered to be wholly satisfactory in only 47% and lacking in one or more respects in 53%. On more detailed analysis there was some deprivation of parental care, such as marital instability or mother working full-time, in 45%; some deficiency of maternal care such as defective diet, clothing, or supervision in 16%; and some social dependence, such as unemployment, in 20%. All three of these unsatisfactory features were present in 8%. This is a rather depressing picture of family life, but, after all, these children were viewed against a background of perfection and most of the imperfections noted, however regrettable, were not serious. Nevertheless, it is rightly claimed that social measurements along such lines are essential for a sound understanding of illness in childhood as well as for rational prevention and treatment. For instance, such a social diagnosis is particularly important in respiratory and alimentary infections, accidents, and enuresis.

Throughout the five years there was no significant relationship between the frequency of calling the family doctor and the Registrar-General's social class or the standard of the mother's care. The family doctor was called to 58% of the illnesses, the figure being approximately the same before and after the introduction of the National Health Service. Children were referred to hospital outpatient departments by family doctors for 17% of illnesses (25% in the first year) and they were admitted to hospital for 5% (11% in the first year). Doctors were much more likely to be called for some illnesses than for others. They were usually called for pneumonia and for illnesses with a rash, but in only half the cases of suppurative otitis media and accident. In the five years only 11 of the 847 children (1·2%) did not receive medical attention at all.

In the five years 56% of the children attended a hospital outpatient department at least once, the attendances being more frequent in the first two years. 90% of the attendances were accounted for by accidents, infections, and questions concerning circumcision and tonsillectomy. 20% of the children were admitted to hospital at least once in the five years. Infective illness accounted for 59% of admissions in the first year, 64% in the second, and 50% in the third; but after the third year there were few for infections and many more for surgical procedures—especially tonsillectomy. Though numerous in the outpatient department, accident cases seldom required admission.

1. Spence, J., Walton, W. S., Miller, F. J. W., Court, S. D. M. A Thousand Families in Newcastle upon Tyne. London, 1954. See *Lancet*, 1954, ii, 371.
2. Growing Up in Newcastle upon Tyne. By F. J. W. MILLER, S. D. M. COURT, W. S. WALTON, and E. G. KNOX. London: Oxford University Press (for the Nuffield Foundation). 1960. Pp. 369. 25*s*.

The acute infectious diseases of childhood were found to be largely independent of social class or family environment, but such was not the case in the important and more serious group of endemic family infections—notably staphylococcal infections, streptococcal infections, tuberculosis, herpes simplex, and infestation with scabies and head lice. These infections tend to involve the family as a whole. They can become established within the family, producing isolated or recurrent acute episodes or chronic illnesses over a long period, and the expression of the infection varies with the age of the individual.

The observations on the development and disorders of speech are of particular interest. A third of the children passed through a period when articulation was so defective that speech was unintelligible. At 5 years, however, 94% had intelligible and fluent speech, while 5% had unintelligible speech and 1% delayed development of language. 37 developed a stammer but in only 1 did it persist beyond the age of 5.

The third and final report covering the school-age period of 5 to 15 years will complete this valuable study, which has already illumined many aspects of child and family life that had long been neglected, but it cannot appear for several years because the children concerned will not reach the age of 15 until the early summer of 1962.

AGE CHANGES IN HUMAN CARTILAGE

HYALINE cartilage has many of the properties of the ideal supporting material for the correction of contour defects by reconstructive surgery. It is used quite extensively for this purpose, but unfortunately the heterogeneous material is often absorbed or replaced by fibrous tissue with loss of its supporting effect. Since the supply of autogenous material is limited, and its provision may be prohibited for other reasons, the suitability of homologous cartilage is being investigated.[1]

As an essential preliminary, Hagerty et al.[1] have studied metabolic aspects of human cartilage, its viability, and its changes on storage and after implantation into volunteers. By counting the cells capable of taking up neutral-red from a dilute solution in Tyrode's fluid, they showed that in specimens removed at necropsy from young adults about 98% of the cells were still viable. With increasing age of the subject, however, there is a sharp fall in the number of cells per unit area. The fall with increasing life-span in the metabolic activity of cartilage, measured by its anaerobic glycolysis, was found to correspond to the fall in cell-count. This indicates that the metabolic activity of the individual cartilage cells changes little with age, the measured decline resulting entirely from the reduced number of cells. The observed fall in potassium also corresponded to this decline in the cell population. Sodium, however, is mainly extracellular and its considerable loss from the cartilage of older subjects is due largely to the progressive dehydration of ageing. By using the potassium content to calculate the volume of the intracellular-fluid compartment, and hence by difference that of the extracellular compartment, Hagerty et al. showed that the loss of sodium with age between 14 and 60 years exceeded by some 21 mEq. per kg. of fresh material that which could be accounted for by the simple reduction in extracellular fluid. The excess must, therefore, have come from the bound sodium, which at the younger age amounts to over 100 mEq. per kg. of fresh material. This loss of bound sodium could be due either to replacement by calcium or to loss of base binding material from the intercellular ground substance. The fall in chondroitin sulphate with age [2 3] is no doubt mainly responsible for the observed fall in bound sodium, and this fall in chondroitin sulphate is itself probably the consequence of the pronounced decline in the cell population.

To what extent these various age changes affect the suitability of cartilage for reconstructive surgery may be shown by the studies on implants into volunteers. In homologous transplants of other tissues viable cells rapidly disappear. With cartilage, however, both histological [4] and metabolic [5] studies suggest that the majority of the transplanted cells survive indefinitely. With human cartilage stored in human plasma at 4°C, Hagerty et al.[6] have found that the viability of the chondrocytes falls to zero after 50 days, but that after 25 days about a third of the cells are still alive. Implants of such cartilage into volunteers for periods ranging from 134 to 1059 days still contained, on removal, an average of 33% of viable cells. Moreover the superiority of these implants over those in which all the cells had been killed by storage in merthiolate saline was clearly shown by the reduction, by a factor of two-thirds, in the degree of fibrous invasion. In view of these encouraging results, further efforts will no doubt be made to improve the viability of the cells on storage.

SENSITIVITY OF GONOCOCCI TO ANTIBIOTICS

STUDIES by Finland and his colleagues in 1950 [7] and again in 1955 [8] failed to reveal any important increase in resistance of gonococci to penicillin or other antibiotics. It was also found that fewer strains were resistant to sulphadiazine in 1953–54 than in 1949. Hirsch and Finland [9] have now investigated the susceptibility to penicillin and twenty other antibiotics and to sulphadiazine of strains of gonococci isolated late in 1958 and early in 1959 from cases of acute urethritis in males.

Each of the agents, except penicillin and sulphadiazine, inhibited all the strains tested within a fairly narrow range of concentrations. Penicillin, erythromycin, and the tetracyclines were the most active of the commonly used agents; whereas polymixin and colimycin were the least active, weight for weight. Hirsch and Finland remark that in-vitro sensitivity by itself is no reliable guide to effectiveness in vivo. Other important factors include the absorption, distribution, and excretion of the drug—and particularly its concentration in the urine and its capacity to penetrate into infected areas. Few, if any, of the antibiotics can be expected to act on intracellular organisms; and secondary infection, particularly with penicillinase-producing staphylococci, may be the cause of some failures with penicillin.

Mr. B. D. FRASER, a deputy secretary in the Ministry of Aviation, is succeeding Sir JOHN HAWTON as permanent secretary of the Ministry of Health. Sir John, who has held this appointment since 1951, is giving it up on medical advice but will undertake special duties in the Treasury.

1. Hagerty, R. F., Calhoon, T. B., Lee, W. H., Cuttino, J. T. *Surg. Gynec. Obstet.* 1960, **110**, 3.
2. Loewi, G. *J. Path. Bact.* 1953, **65**, 381.
3. Kaplan, D., Meyer, K. *Nature, Lond.* 1959, **183**, 1267.
4. Dupertuis, S. M. *Arch. Surg.* 1941, **43**, 32.
5. Laskin, D. M., Sarnat, B. G., Bain, J. A. *Proc. Soc. exp. Biol., N.Y.* 1952, **79**, 474.
6. Hagerty, R. F., Calhoon, T. R., Lee, W. H., Cutting, J. T. *Surg. Gynec. Obstet.* 1960, **110**, 277.
7. Gocke, T. M., Wilcox, C., Finland, M. *Amer. J. Syph.* 1950, **34**, 265.
8. Love, D. B., Jr., Finland, M. *A.M.A. Arch. intern. Med.* 1955, **95**, 66.
9. Hirsch, H. A., Finland, M. *Amer. J. med. Sci.* 1960, **239**, 41.

Special Articles

THE CONCEPT OF EGG YOLK AS A DIETARY INHIBITOR TO RHEUMATIC SUSCEPTIBILITY

ALVIN F. COBURN
M.D.

ASSOCIATE PROFESSOR, DEPARTMENT OF PEDIATRICS,
NEW YORK MEDICAL COLLEGE, NEW YORK 29, U.S.A.

"Certainly, if I had to start again the weary struggle with rheumatism, I should have to reconsider my views on nutrition. . . . Under-nutrition may be general or special and bids me at the moment tread with caution, for we shall learn much more about this in the future."—F. J. POYNTON (1938).

THE past two decades have seen the establishment of the hæmolytic streptococcus as the factor of infection in the rheumatic state (Coburn 1931) and the prevention of rheumatic recurrences by antibacterial prophylaxis (Coburn and Moore 1939, Thomas and France 1939, Rammelkamp 1955-56). In sharp contrast to these advances has been the lack of progress in defining the factors which determine rheumatic susceptibility. It is generally recognised that rheumatic fever is limited to less than 5% of the population, those with a "diathesis." This appears to be a genetic abnormality, probably manifest in biochemical disturbances: for example, a difference in lipid metabolism between rheumatic subjects and their non-rheumatic siblings has been reported (Chang et al. 1957). Yet there is no knowledge of dietary needs during infancy and childhood peculiar to the rheumatic subject.

In this paper I recapitulate and discuss observations showing that: (a) inadequate nutrition is part of a poor environment; (b) rheumatic-fever children usually lack sufficient eggs in their diets; (c) the escape from poverty is followed by an increase in the consumption of eggs and a decrease in the incidence of rheumatic fever; (d) supplementation of children's diets with egg yolk or certain fractions thereof is followed by decreased rheumatic susceptibility; and (e) there is a fraction of egg yolk which in extremely small amounts has been found to have high antiallergic activity in laboratory animals.

Some Effects of Loss of Poverty

In childhood, high morbidity-rates for rheumatic fever are associated with poverty. In London, poverty is accompanied by a "bad micro-climate" (Poynton 1938). In New York, the association between home environment [1] and the incidence of rheumatic fever can be clearly envisaged at the intersection of Park Avenue and 96th Street (Coburn 1958). South to 46th Street, both sides of Park Avenue are solidly built with luxurious skyscraper dwellings which house large numbers of children. Nowhere in New York City are families more wealthy. The northern part of Park Avenue, on the other hand, has for many years been a slum area solidly built with five-storey tenements. Whereas rheumatic fever has long been prevalent north of 97th Street, it is rarely seen by pædiatricians practising south of the intersection (Mason 1958).

The present study began in 1947 in Chicago. Rheumatic fever was particularly prevalent in the Stockyard area (Bridgeport district) with its population of some 50,000.[2] These were families with many children, all Caucasian but of many national backgrounds—Polish, Lithuanian, German, Italian, and so on. Their diets differed according to ethnic background, but up till 1941 they had little money to feed many mouths. After world war II their fortunes changed precipitously. Not having to pay higher rent at that time, they spent their larger incomes on more and better foods, including luxury items.

Since the rheumatic children and their parents were continuously under my care, it was possible to detect most of their streptococcal infections. For the purposes of this study non-suppurative infections were treated symptomatically without antibiotics or sulphonamides. The expected incidence of group-A streptococcal nasopharyngitis with the serological types prevalent in Chicago did occur in these rheumatic families; but rheumatic recurrences almost disappeared. By 1955, after several years without recurrences, there seemed to be no further need for this rheumatic-fever clinic. The most striking fact in the five years before the clinic was closed was the disappearance of initial rheumatic attacks. I did not see a single new case of rheumatic fever among the hundred rheumatic families under observation, even though a large number of younger siblings contracted streptococcal infections. This raised the question: Had group-A streptococcus lost its "rheumatogenicity" or had some environmental factor associated with the large rise of income modified host reactivity in a way that made the children less susceptible to rheumatic fever?

It so happened that this study was paralleled by a simultaneous survey of rheumatic fever at an all-Negro grade school nearby. There, the family income remained extremely low, and the incidence of the disease remained high. Likewise, about two miles away, in my rheumatic-fever clinic at the Cook County Hospital, new cases of rheumatic fever became relatively rare in the higher-paid Caucasian groups but did not change in the under-privileged Negro community. As a result, by 1954-56, the clinic population was mostly Negro. The streptococcus had *not* lost its "rheumatogenicity" among the poor Negro families living in areas near the Caucasian Bridgeport district where poverty had considerably lessened.

Although one cannot exclude the importance of unknown environmental changes, it was possible to show what happened to the diets of these children when income increased more rapidly than living costs. I limited myself to boys and girls aged 7–15, divided for diet studies into three age-groups, 7–9, 10–12, and 13–15. No data were obtained on infant feeding, though its significance to maturation of the rheumatic process is recognised.

1. Breast-feeding of infants has usually accompanied a "bad micro-climate", whereas bottle feeding has become a characteristic of infant feeding where home environment conditions are excellent. For example, one pædiatrician with a wealthy Park Avenue private practice below 96th Street reported that breast-feeding was a rarity among his patients in the period 1932–41 (Weisman 1959). Recently it has been pointed out that breast-feeding has for two decades been decreasing among all American mothers; "in America only 1 in 5 has breast-feeding at the end of the lying-in period" (Hytten 1959). Attention is called to this point because of the possibility that infants who are breast fed may have lower blood-lipid levels than those fed with cows' milk (Zarafonetis and Kalas 1958).

2. A house-to-house survey was made during the summer of 1947, and every family in the Bridgeport district was questioned in its native language. Information was obtained on the incidence of hospitalised cases of rheumatic fever, the accuracy of which was checked by medical personnel. Lay volunteer workers from social service agencies obtained collateral information on location at time of first rheumatic attack, income, duration of residence, occupation, size of family, number per room, food preferences, schools attended, and other matters of general public-health interest.

TABLE I—VARIATIONS IN DIETARY CONSTITUENTS AMONG 1039 CHILDREN OF DIFFERENT INCOME AND AGE-GROUPS
Percentage Meeting Recommended Allowances *

Group	Ages	No. of children	Eggs †	Milk ‡	Total protein	Animal protein	Vitamin A	Vitamin C
a. Grade-school children in poverty	7–9	123	89	19	33	62	6	1
	10–12	155	82	12	17	60	5	10
	13–15	109	90	3	23	44	5	6
b. Quiescent rheumatic children in poverty	7–9	49	86	53	53	78	17	24
	10–12	59	85	67	52	79	15	22
	13–15	45	74	19	23	53	11	22
c. Non-rheumatic children after 5 or more years at moderate economic level	7–9	169	100	59	68	65	32	71
	10–12	138	100	72	79	71	32	68
	13–15	192	100	37	35	100	33	69

* Requirements for eggs and milk are unknown.
† Percentage receiving any eggs, excluding prepared foods.
‡ Percentage receiving milk, 3 cups ages 7–9, 4 cups ages 10–15.

Dietary information from the rheumatic subjects and their siblings was obtained by three methods:

1. A dietary history was taken at the clinic by skilful interviewers—a nutritionist and a nurse.

2. A food recall method was used by the nutritionist and nurse to determine the previous twenty-four hour intake of foods.

3. A questionnaire booklet was given to families for each child, to cover a seven-day period. In this booklet the food records were maintained by each individual for himself and then checked by interview with the nutritionist and nurse.

For the purpose of this study, the food intakes were tabulated in groups of foods.[3]

The diets were tabulated for servings of milk, including cheese and foods made with milk; meat including fish and fowl; liver; eggs; enriched grains and cereal products; non-enriched grains and cereal products; cakes and cookies; candy bars; legumes; potatoes; fruits and vegetables high in carotene; fruits and vegetables high in ascorbic acid; total servings of fruits and vegetables. Soft drinks, tea or coffee, and medications used as nutritional supplements were listed. The only nutrient which was calculated was protein. Experience of others has shown that an approximation of the protein intake provides a good indication of the adequacy of niacine, thiamine, and iron. Tabulation of the milk intake provides an indication of the calcium and riboflavine content of the diet. Vitamin A, carotene, and vitamin-C contents of the diet were estimated by calculations of fruits, vegetables, and liver.

Three groups of children, divided as to economic and health status, are shown in table I:

Group a are an average grade-school population living in poverty, typical of the Stockyard area of Chicago in 1947.

Group b are quiescent rheumatic children, of the same economic level sharing the " bad micro-climate " of the Bridgeport district. They had attended cardiac-school classes and had had many months' association with doctors, nurses, and dieticians in hospitals and convalesent homes.

Group c are with 2 exceptions, non-rheumatic. The children had " graduated " from low to moderate incomes but still occupied quarters typical of the Bridgeport district. Their families had spent their increased earnings on food rather than on more expensive homes in the suburbs.

With increased income there is a striking rise in the proportion of children receiving adequate amounts of vitamins C and A, total protein, milk, and eggs.[4] In the case of eggs, all children whose families had a marked rise in income (group *c*) ate at least one egg a week; whereas 14–26% of the rheumatic poor children (group *b*), and 10–18% of the unselected poor children (group *a*) had less than one egg a week (table I). Furthermore, when families of children could afford it (group *c*) each child consumed, excluding eggs used in cooking food, between 4·0, 4·1, and 4·7 eggs (mean value) per week in the three age-groups studied.

Children who developed rheumatic fever (group *b*) had better diets, even though their financial condition was unchanged. But, though they got more milk, total protein, animal protein, vitamin A, and vitamin C, they did not get more eggs. For each age-group the consumption of eggs was lower among the rheumatic children than among their schoolmates. This finding is in accord with the observations of Wallis (1954), who pointed out a dislike for eggs in rheumatic-fever subjects.

TABLE II—STATISTICAL ANALYSIS OF DIETS IN THREE GROUPS OF CHILDREN (THREE AGE-GROUPS COMBINED)

—	(*a*) Grade-school children in poverty		(*b*) Quiescent rheumatic children in poverty		(*c*) Non-rheumatic children after 5 or more years of relative prosperity	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Eggs (per week)	3·5	±3·0	2·8	±2·7	4·3	±3·2
Milk (cups per day)	2·0	±0·9	3·1	±1·2	3·6	±1·1
Total protein (g. per day)	62·6	±13·4	69·4	±14·1	73·1	±15·7
Vitamin A	2·7	±2·2	3·6	±2·5	6·0	±3·5
Vitamin C	2·7	±2·5	3·7	±2·8	9·4	±4·3
No. of subjects	387		153		499	

Table II shows the average consumption of each of the five foods in each of the three groups.

After children of poor families (group *a*) had recovered from rheumatic fever (group *b*) their diet was better. Diet also improved when poor families (groups *a* and *b*) emerged from poverty (group *c*).

Whereas the environment was not obviously improved when children with rheumatic fever (group *b*) returned to their homes, there was a statistically significant increase in their consumption of all foods studied, except eggs. Moreover, there was also a statistically significant difference between the low egg consumption of the poor rheumatic children (group *b*) and the relatively high egg consumption of the children of families in moderate financial circumstances (group *c*). The differences in mean consumptions of each food for each pair of groups (group *a v.* group *b*, group *b v.* group *c*, group *a v.* group *c*) were tested statistically. All comparisons were

3. Wilcox and Galloway (1954) determined food consumption in terms of nutrients as calculated from seven-day records in Utah children. Among these were 131 rheumatic subjects paired with 131 controls of the same economic level. In this study, a statistically lower consumption of calories and five nutrients was found for the rheumatic girls. However, the differences among the boys was not statistically significant. Although the rheumatic group fulfilled the recommendations of Jackson and Kelly (1949) for meat, fish, poultry, and some fruits, this group failed to meet the requirements for milk, eggs, and tomatoes. In contrast to the controls who disliked liver and several other foods, 10% of the rheumatic subjects expressed a dislike for certain vegetables and eggs.

4. Previous studies indicated that supplementation of diets with other foods had no detectable effect on susceptibility to rheumatic recurrences. Items tested individually for a period of one to three years on rheumatic children were vitamin A, vitamin C, milk, and the protein of egg yolk.

statistically significant at the 1% level ($P < 0.01$). These tests are summarised:

Group *a* *v.* group *b*.—The mean consumption of each food (except eggs) is higher for group *a*. Egg consumption is significantly lower for group *a*.

Group *b* *v.* group *c*.—The mean consumption of each food is higher for group *c*.

Group *a* *v.* group *c*.—The mean consumption of each food is higher for group *c*.

Possible Association Between Lack of Eggs in Childhood and Rheumatic Fever

It was seen in table I that 10–18% of Chicago children in poverty (group *a*) had no eggs in their diets except in prepared foods. For quiescent rheumatic children, also in poverty (group *b*), the figure was 15–26%. The mean values for eggs consumed per week, according to age, for the three groups of children studied are shown in table III. The proved rheumatic subjects (group *b*) consumed the least eggs. Next in consumption were the underprivileged children (group *a*). In this group the incidence of rheumatic fever was 2·8%; whereas among children of group *c*, who ate the most eggs, it was only 0·6%. A survey of group *c* families showed that before the escape from poverty, they had experienced a high incidence of

TABLE III—EGG CONSUMPTION BY AGE IN THREE GROUPS OF CHILDREN

Age	No of children	Eggs per week	S.D.
Group a :			
7–9	123	3·4	±2·8
10–12	155	3·5	±3·0
13–15	109	4·3	±3·1
Group b :			
7–9	49	2·8	±2·1
10–12	59	2·7	±2·9
13–15	45	3·0	±3·0
Group c :			
7–9	169	4·0	±2·6
10–12	138	4·1	±3·0
13–15	192	4·7	±3·2

rheumatic fever. Group *c* had a familial history of at least 12% among the preceding generation—parents and their siblings. It was estimated that during the years 1920–40, when this generation had been underprivileged children, they had had an incidence of rheumatic fever of about 3%.

The above findings among Chicago pupils are in accord with the possibility that there may be an association between poverty, low consumption of egg yolk during childhood, and maturation of the rheumatic process.

Nutritional surveys were also made in New York City before the war. The diets of wealthy Brearley School girls, among whom there had been no case of rheumatic fever in ten years, were compared with the diets of poor rheumatic-fever children living near this school. The diets of the Brearley School girls were adequate in all respects, including the daily consumption of eggs; whereas the rheumatic children had multiple dietary deficiencies and few eggs (Coburn and Moore 1943).

Supplementation of Diets with Egg Yolk

Meanwhile, supplementation of diets was tested in small groups of rheumatic children. In New York City the supplement was eggs or whole powdered egg yolk, while in Chicago it was fractions of powdered egg yolk.

1. For two years 30 children at a convalescent rheumatic home received four egg yolks daily. No other change in diet was made and no antibacterial drugs were given. 22 of these children contracted 24 proved group-A streptococcal infections with many serological types (Coburn 1945), but none showed clinical evidence of rheumatic recurrences. This was in sharp contrast to previous experience in the convalescent home, where rheumatic recurrences had been seen each year (Coburn and Pauli 1935).

2. Rheumatic boys and girls living at home in New York City also received food supplements. No prophylactic drugs were given, but 60 children had supplements (including eggs) during winter and spring months, while 29 served as "controls". The clinical results were:

i. Of the 29 children on their normal diet (many deficiencies) 11 had a recurrence.

ii. Of the 35 children whose normal diet was reinforced daily with two eggs, a quart of milk, meat, butter, halibut-liver oil, 'Viosterol', &c., 3 had a recurrence.

iii. Of the 25 children whose normal diet was reinforced only with powdered egg yolk (equivalent to six eggs daily), 1 had a recurrence.

3. A two-year study was made of the effect of giving egg-yolk powder (equivalent of four egg yolks daily) to rheumatic children for three to four weeks after they developed hæmolytic (group A) streptococcal pharyngitis. No medication was given during this period. Of 28 receiving this supplement, only 1 showed fresh rheumatic activity, whereas among 28 "controls" on their normal diets (which had many deficiencies) 10 showed it.

4. A one-year study in which about 40 rheumatic children (many dietary deficiencies) received a daily supplement of only the protein fraction from four egg yolks was discontinued because of rheumatic recurrences.

5. Finally, in a four-year study made in Chicago in 1952–56, the normal (deficient) diet of 45 rheumatic children was reinforced with egg-yolk alcohol-soluble material (A.S.M.) produced by Dr. Claire Graham of Wilson Laboratories (Coburn, Graham, and Haninger 1954). No other changes in their inadequate diets were made; no sulphonamides, antibiotics, or other significant drugs were administered. On the average, 35 highly susceptible rheumatic subjects received the supplement throughout the school year, September to July. The equivalent of six egg yolks was advised; and about half of this was actually consumed, in the form of an elixir taken twice daily. All but one of these rheumatic children were under fifteen years of age.

During the four years 45 children, considered highly susceptible rheumatic subjects, were given this material. A minimum of 17 attacks was expected among them after streptococcal infections, but only 5 occurred.

The data obtained under these various conditions, both in New York and a decade later in Chicago, were found to be statistically significant. However, from the viewpoint of the statistician, the experimental design was not ideal.

Anti-allergic Activity of Egg-yolk Substances

Experimental findings clearly indicate that there is at least one antianaphylactic substance in egg-yolk alcohol-soluble material, which appears to be absent from the protein or acetone-soluble material (Coburn et al. 1954). This finding has been confirmed and extended in several laboratories by measuring joint and skin lesions in either the Arthus or tuberculin reaction.

French and Allen (1955) showed that the reverse Arthus reaction could be used successfully to demonstrate the anti-inflammatory effects of egg-yolk phospholipid fractions. Chang and French (1956) found that the active material was in the A.S.M., absent from the protein and acetone-soluble fractions, and that the anti-inflammatory effect did not appear to be mediated by the adrenals. Following the important work of Long and Martin (1956), Kuehl et al. (1957) identified in egg yolk N-(2-hydroxyethyl)-palmitamide as a natural occurring anti-inflammatory agent. Later, Ganley and his associates (1958) in a wide variety of tests studied the anti-inflammatory activity of compounds obtained from egg yolk, peanut oil, and soybean oil. Their crystalline fractions from three sources were all identified as N-(2-hydroxyethyl)-palmitamide. They were active (antianaphylactic) at 0·3 μg. per kg. body-weight.

This work was extended by Ganley and Robinson (1959). Instead of the Arthus reaction (joint swelling) in the guineapig they studied systemic anaphylaxis in the mouse. Approximately 50 μg. per kg. (1 μg. per 20 g. mouse) gave survival-rates comparable to those obtained after treatment with 100 to 200 mg. hydrocortisone per kg. body-weight.

Discussion

The lack of a suitable experimental animal has prevented direct attack on the factors which determine susceptibility to the rheumatic state. The approach has had to be circuitous, by collecting observations on human subjects. Among findings made indirectly, one is impressed with the circumstantial evidence that poor nutrition in early childhood may determine whether the genetically susceptible child either escapes or enters the rheumatic state. One food, which in the past has been expensive and not consumed abundantly by rheumatic-fever children is egg yolk. What metabolic functions are entered by constituents of the egg are unknown. Egg yolk is high in phospholipid; its antiallergic activity is in the alcohol-soluble fractions containing lecithin and sphingomyelin (Coburn et al. 1954); the blood-level of these two lipids is lower in the rheumatic subject than in non-rheumatic siblings (Appleton et al. 1959), as is true also for total lipids, phospholipids and cholesterol (Chang et al. 1957).

It is recognised that egg yolk probably has no effect on rheumatic manifestations. Furthermore, evidence collected in military and civilian populations suggests that when the host has passed puberty the consumption of egg yolk may not suppress maturation of the rheumatic process. Nevertheless, the cumulative evidence does indicate an association between egg consumption *in childhood* and the degree of susceptibility to rheumatic recurrences. This evidence is circumstantial. There is need for definitive studies of sufficient magnitude and duration—in areas where poverty is great, antibiotics are not available, and streptococcal infections of the upper respiratory tract are prevalent—to provide statistically valid information on whether egg-yolk substances given abundantly in infancy protect against the rheumatic state.

The critical problem remains: What determines whether the child infected with hæmolytic streptococcus enters the rheumatic state? At this time, the concept that one or more factors in egg yolk may inhibit maturation of the rheumatic process may seem like grasping blindly at a delicate straw. But, who would ever have envisaged the beneficence of cowpox?

Summary

1. Most children who developed rheumatic fever before puberty had had inadequate diets in childhood, including a low egg consumption (table I).

2. In the years after they had been in hospital for rheumatic fever, there was a striking increase in their consumption of all foods except eggs. Comparing these quiescent rheumatic children with their non-rheumatic siblings, their egg consumption was consistently lower. This difference was significant statistically at the 1% level (table II).

3. Also statistically significant ($P < 0.01$) was the higher consumption of egg yolk and other foods in families who had escaped poverty, as compared with rheumatic and non-rheumatic families in poverty.

4. General improvement in diet during childhood (other recognised factors of the poor environment being apparently unchanged) was followed by a lower morbidity-rate for rheumatic fever. Compared with the underprivileged families from which the rheumatic fever children came, the families which had emerged from poverty had a strikingly lower incidence of rheumatic attacks.

5. Throughout these studies the low consumption of eggs seemed to be associated with a high incidence of rheumatic recurrences.

6. After the diet had been supplemented with whole egg yolk or the alcohol-soluble fraction thereof, rheumatic recurrences fell below the expected number.

7. An antiallergic component of the alcohol-soluble fraction has been isolated, identified, and synthesised. Its action in laboratory animals against the immediate and delayed types of hypersensitivity reactions is described.

8. The possible effect of egg-yolk ethanolamine palmitamide as a dietary supplement is being tested among children of the poor in New York City.

9. The underlying biochemical mechanism of the rheumatic state and its relation to nutrition in infancy remain to be determined.

This work was supported by grants from the Easter Seal Research Foundation and the New York State chapter of the Arthritis and Rheumatism Foundation.

I am indebted to Mr. Herbert Rich, of the New York Medical College, for making the statistical analyses.

REFERENCES

Appleton, H. D., Coburn, A. F., Meltzer, Y. L. (1959) *Clin. Chem.* **5**, 557.
Chang, I., French, C. E. (1956) *Proc. Soc. exp. Biol., N.Y.* **93**, 366.
— Coburn, A. F., Pargellis, P. (1957) *Amer. J. med. Sci.* **234**, 78.
Coburn, A. F. (1931) The Factor of Infection in the Rheumatic State. Baltimore.
— (1945) *Amer. J. Dis. Child.* **70**, 339.
— (1958) *Arch. int. Rheum.* **1**, 631.
— Moore, L. V. (1939) *J. clin. Invest.* **18**, 147.
— — (1943) *Amer. J. Dis. Child.* **65**, 744.
— Pauli, R. H. (1935) *J. exp. Med.* **62**, 129.
— Graham, C. E., Haninger, J. (1954) *ibid.* **100**, 425.
French, C. E., Allen, J. R. (1955) *Proc. Soc. exp. Biol., N.Y.* **87**, 41.
Ganley, O. H., Graessle, O. E., Robinson, H. J. (1958) *J. Lab. clin. Med.* **51**, 709.
— Robinson, H. J. (1959) *J. Allergy*, **30**, 415.
Hytten, F. E. (1959) *Amer. J. clin. Nutrit.* **7**, 259.
Jackson, R. L., Kelly, H. G. (1949) *J. Amer. dietet. Ass.* **25**, 392.
Kuehl, F. A., Jr., Jacob, T. A., Ganley, O. H., Ormon, R. E., Meisinger, M. A. P. (1957) *J. Amer. chem. Soc.* **79**, 5577.
Long, D. A., Martin, A. J. P. (1956) *Lancet*, i, 464.
Mason, H. H. (1958) Personal communication.
Poynton, F. J. (1938) Proceedings of International Congress on Rheumatism and Hydrology and the Bath Bicentenary Congress on Chronic Rheumatism, p. 174.
Rammelkamp, C. H., Jr. (1955–56) *Harvey Lect.* **51**, 113.
Thomas, C. B., France, R. (1939) *Bull. Johns Hopk. Hosp.* **64**, 67.
Wallis, A. D. (1954) *Amer. J. med. Sci.* **227**, 167.
Weisman, D. (1959) Personal communication.
Wilcox, E. B., Galloway, L. S. (1954) *J. Amer. Dietet. Ass.* **30**, 345.
— — (1954) *ibid.* p. 453.
Zarafonetis, C. J. D., Kalas, J. P. (1958) Personal communication.

PRESCRIBING RESTRICTIONS IN AUSTRALIA

FROM AN AUSTRALIAN CORRESPONDENT

THE new Australian pharmaceutical benefit book issued on March 1 demonstrates how quickly a free drug scheme can grow in size and complexity. Originally introduced in 1950 as a scheme to supply free a few lifesaving drugs to the general public and a limited formulary to what were then "a few" pensioners, the scheme has rocketed from £3 million to £27 million a year, due to (1) the addition of new costly drugs, such as the oral diuretics and newer antibiotics, and (2) the great increase in the number of pensioners.

The object of the amended Health Act which precipitated this new issue was, firstly, to widen the scope of drugs prescribable under this scheme, so that practitioners might be encouraged to return to using the cheaper forms of drugs listed in the *B.P.*; and, secondly, by

imposing a 5s. fee on all scripts except pensioners' to recoup some loss and deter unnecessary prescribing.

The book is divided into several sections. The first gives 62 administrative clauses, the second a schedule of ready prepared items, mostly single drugs, numbering 962, which may be prescribed in the nominated form only, uncompounded and with certain restrictions. The restrictions are: some only for pensioners, others for specific diseases, others for children only, some only with special authority. The number that can be presented and the number of repeats, if any, are defined. The third section lists some 500 items which may be used in extemporaneous preparations. There are set limits to amounts that can be prescribed and repeated in this section also. The fourth section is a small formulary called a prescribers' list, which, it is suggested, should be used where possible. The last section is several pages of restricted benefits listed in previous sections and what they are restricted to. There is also a separate booklet of proprietary preparations listed numerically and alphabetically. Throughout the book the price of the item recoverable by the chemist is listed.

Will such a formidable prescribers' book work satisfactorily? Once it has been read and learnt, it should. But it will be some months before all practitioners are familiar with it.

The main criticisms of the scheme are:

(1) Its complexity.

(2) The almost total exclusion of the compounded tablet, despite the increasing popularity of this method of prescribing, with its virtue of stability and often greater economy than multiple tablets and mixtures.

(3) The unfairness, in that some patients with certain diseases get everything, while others get very little if anything.

(4) The exclusion of such drugs as reserpine, chlorpromazine, and butazolidine (restricted to pensioners), and most anti-histamines.

(5) The severe limitations on amounts prescribable, thus often making it as cheap for the patient to obtain his prescription in the ordinary way.

From the chemists' point of view it means lower margins generally, and a lot more paper work. The wholesale druggists must come down to the lowest produced figure to be included, unless they have a monopoly of the drug. From the practitioners' viewpoint there will be a good deal more work in prescribing till he has become familiar with the scheme. For the patients, prescription costs for allowed drugs will average much the same as before, but those that were not free may now cost more in some cases.

Reconstruction

BEDS AT HOSPITAL AND BEDS AT HOME

The Future of General Practice

IN 1948 the hospitals were the axis of medical care in this country. By enabling everybody to have a personal physician, the National Health Service was intended to change their dominating role: specialist care was to be recognised as episodic and incidental to the general medical care provided by the general practitioner with his supporting domiciliary services. But Mr. Gordon Forsyth and Dr. Robert Logan, in their important new study made for the Nuffield Provincial Hospitals Trust,[1] conclude that practice has not yet caught up with the fundamental theory of the N.H.S. Though the cost of hospital care is high and rising, there has been little change either in the hospitals' conception of their place in the scheme of medical care or in the public's attitude to them.

This research on the hospital needs of an area has been very usefully amplified into an exploratory study of some of the factors involved in planning the future of the Health Service, and on the role of the practitioner. In the concept of comprehensive medical care embodied in the N.H.S., it is the practitioner who should decide whether or not the patient requires hospital care or investigation: "in this sense, therefore, the general practitioner is instrumental in determining the case-load to be borne by the hospitals". The introduction to the report quotes a statement that "greater savings could be achieved in a hospital service by improving the quality of general practice than by any other single move".[2]

DEMAND FOR BEDS

Estimates made jointly by the Ministry of Health and the Nuffield Provincial Hospitals Trust in 1941–44 ranged from 450 to 640 acute general hospital beds per 1000 population. But the Trust's surveys in 1950–51 at Norwich and Northampton[3] suggested that in these places the figure might be only about 200. These findings clearly had many implications for those planning hospital services, and further surveys were arranged to take place in industrial areas. The one by Mr. Forsyth and Dr. Logan is the first of these, carried out at Barrow-in-Furness by the University of Manchester in arrangement with the Manchester Regional Hospital Board.

Although the bed/population ratio these investigators suggest for Barrow is some 25% higher than the estimates for Norwich and Northampton, it generally supports the belief that the demand for acute hospital care can be satisfied with about 250 beds per 100,000 (at present the actual provision in England and Wales is 310)—in other words about half the beds thought necessary at the start of the N.H.S. The importance of finding the right number is evident from the fact that an over-provision of 1 bed per 1000 would mean for England and Wales a total of 45,000 additional beds—equivalent to 100 hospitals, whose capital cost at present prices would be about £225 million. The report mentions that between 1937 and 1957 the average stay in acute beds fell from 13 to 7 days in the United States and from 14 to 12 days here.

CLINICALLY UNNECESSARY ADMISSIONS

But how far does the actual present demand equate with clinical need? Discussions in the wards led to the conclusion that at Barrow 40% of the women in medical beds did not—on clinical grounds alone—require inpatient care; and in a further 15% their need of it was doubtful. The corresponding estimates for men were 25% and 21%.

When the critical number of beds is adjusted accordingly, Barrow is seen to require 2·3 beds per 1000 population instead of 2·5.

"The difference between the critical number and the adjusted figure reflects the impact of conditions external to the hospital service—local housing conditions, availability of domiciliary services, attitudes of general practitioners and so on. In other words, even patients suffering from the same disease may vary in the demands they make on the hospital, and the

1. The Demand for Medical Care: a study of the case-load in the Barrow and Furness group of hospitals. By GORDON FORSYTH, B.A., and R. F. L. LOGAN, M.R.C.P. London: Oxford University Press. 1960. Pp. 153. 7s. 6d.
2. Fleming, C. M. W.H.O. Symposium on the Relations Between the Hospital and its Community. Stockholm, Nov. 3, 1958.
3. Studies in the Functions and Design of Hospitals. London, 1955.

variation depends on their social circumstances" . . . In Barrow these circumstances, in general medicine and surgery and pædiatrics, "inflate demand to the order of 8 per cent. or 0·2 acute beds per 1000 population".

But the decision to admit to hospital is often not rational: it is usually a matter of custom and tradition; and, rather than the home nursing facilities of Barrow being inadequate, "there was lack of awareness by the general practitioner and others of their full potential".

"In the long run", Mr. Forsyth and Dr. Logan ask, "would it be a good thing to pare down the hospital inpatient facilities until they accorded with the medical needs as envisaged above?"

"We cannot be at all sure that, however it is organised, general practice will fulfil its theoretical promise within the National Health Service. No public service operating on a national scale can hope to recruit the necessary number of altruists, and medical schools are only just beginning to think of teaching medical care outside hospital."

An attempt at Barrow to relate practitioners' use of hospital to the size of their lists, and the location and type of their practices, "cast doubt on the assertions that a reduced hospital case-load could be effected by alone raising the capitation fees and reducing the average size of practice list". The investigators got no support, either, for the view that practitioners who use direct-access diagnostic facilities most send fewest patients to hospital, or that relatively expensive prescribing may be offset by smaller use of hospital beds.

GENERAL PRACTICE IN N.H.S.

In their conclusions Mr. Forsyth and Dr. Logan speak of doubts [4] whether the general practitioner, if he continues in his present role and skills, has any really useful part to play in comprehensive medical care. "The argument runs that in the past two decades medical knowledge has expanded so rapidly that it can only be applied effectively by the specialist." But they also quote the Cohen Committee of 1954, which said that "the general practitioner service is an essential not a subordinate service, indeed, in a sense the general practitioner must hold the key position in the Health Service". Systems of medical care are called on to face the problem of all large-scale organisations where there is a high degree of division of labour—someone has to integrate the activities of the specialists.

On the operation of the N.H.S. in its first decade they make the following three broad comments:

(1) It is all very well in theory to cast the general practitioner as the leader of the new advances in preventive medicine because he has the best chance of undertaking presymptomatic detection. But has he the necessary clinical skill to take up the challenge? The death-rate from coronary thrombosis in middle-aged men, with anticoagulants available, suggests that he has not. Again, one-fifth of diabetics are undiagnosed and untreated until they present complications. In mental illness some 25% of cases in general practice are emotional rather than physical and many go undiagnosed until the manifestations become sufficiently serious to project them into the mental therapy service.

(2) It must be confessed also that the removal of the general practitioner from the hospital as a consequence of the regional spreading of consultant services has not helped him to keep in touch with technical advances which have been applied in the hospital and not in general practice . . . the average duration of stay in British hospitals continues to be much longer than in North American hospitals, and one of the reasons, as we have shown in Barrow, is the failure of the general practitioner to integrate the hospital and domiciliary services, for it is at the point of integration that the Health Service has been least successful.

(3) Even in that sphere becoming peculiar to British medicine, the activities involved in the emotional term "family doctor", certain aspects of the Health Service suggest that after all the general practitioner is not operating as the kingpin of the system. For example, the consultants established in the provinces are general consultants and are far less specialised than their teaching hospital colleagues. Furthermore the development of almoner and social services attached to the hospitals, and functioning to assist the consultant to relate his treatment to the patient's social and domestic circumstances, can be taken as a reflection of the general practitioner's failure to provide the necessary link between treatment, aftercare, and rehabilitation.

The way in which the Health Service has developed in relation to general practice is not, they feel, encouraging. "If there is really to be a renaissance of general practice, instead of merely lip-service to the general practitioner, then efforts must be made to bring the general practitioner back to the hospital, perhaps with an extension of clinical assistant posts, accompanied by modifications in the method and incentives of remuneration."

4. Silver, G. A., *Yale J. Biol. Med.* 1958, **31**, 29. See *Lancet*, April 2, 1960, p. 748.

Medicine and the Law

Fatal Shock from a Cardiac Monitor

WHILE being prepared for a lung operation in the London Chest Hospital, a patient died on the operating-table when he received a 325-volt shock from a cardiac monitor.[1] At the inquest on April 4 it was stated that one electrode had been attached to the patient's thumb, one to his head, and a third diathermy plate-electrode to his right leg. This third electrode was connected to the case of the instrument, which was assumed to be at earth potential. When the instrument was switched on, the patient moved but, as this usually happens, no particular notice was taken. Something was clearly amiss, however, when the surgical registrar received a shock of "some magnitude" from the patient.

An electrician who examined the monitor found that the case was not earthed and that there was a broken wire inside. Apparently the earthing-connection to the case had been omitted in error, although the instrument had been repaired by the manufacturers at least twice. If the plate-electrode had not been fixed to the patient, it is unlikely that he would have received a shock.

This seems to be the first reported mishap caused by a cardiac monitor, but it has disquieting implications, particularly since the instrument was a commercial product and not one of the "home-made" instruments that often attract criticism. Pre-amplifiers and first-stage amplifiers should be transistorised, and even if the electrocardiogram is to be displayed on a cathode-ray tube, the difficulties of keeping high potentials where they belong are not insuperable: "hybrid" circuits are perfectly satisfactory in practice. Whenever an earthed, rather than an "earthy", electrode is thought to be necessary, some means should be provided for testing for earth-continuity. A suitable circuit is shown in the report of the working party on anæsthetic explosions.[2]

1. *Times*, April 5, 1960.
2. Report of a Working Party on Anæsthetic Explosions; p. 32. H.M. Stationery Office. 1956.

In England Now

A Running Commentary by Peripatetic Correspondents

Is it possible that some of today's psychological disturbances are due less to the higher cerebral centres being over-used in reasoning than mis-used in predicting? If so, road-users (which most of us are) should be the first to suffer, because torrents of sensory data about hurtling traffic, flashing lights, and suicidal pedestrians pour ceaselessly into their sensorium, which has urgently to receive, digest, analyse, and then to predict and act upon the result.

This frenzied cerebral stimulation now plays a major part in our lives, and in our deaths, and descends in an avalanche on a brain not designed to cope, at least not often, with objects moving faster than the human body. The original cerebrum as issued to the Neanderthal gent was adequate enough for his "solitary, poor, nasty, brutish, and short" life, whose tempo reached maximum brio with a defiant rock hurled at a passing pterodactyl, or some deft footwork during cultural exchanges with stone-axes and the tenants of the next cave. Even then, such momentary and infrequent frolics involved quantities which were readily calculable and results which were easily predictable by contemporary grey and white matter, even when housed in a brain-pan so shallow that when its owner yawned, the contents slopped over the sides.

Today's integrations require a brain-pan with the dimensions of the Jodrell Bank telescope. Luckily, according to the doctrine of the survival of the fittest, our descendants should get better and better at prediction, and will eventually be able to tell their own fortunes, which should therefore be pretty prosperous ones.

* * *

In the old days if you developed, say, a small rash on one of your legs you showed it to your doctor, and he would say: "That's nothing to worry about. Get yourself a small tin of zinc ointment, and it'll clear up in a day or two." So you went to a chemist and bought a 2*d.* tin; and at the end of three days, when your rash had gone, you used the rest to lubricate the wheelbarrow or the latch of the garden shed.

Nowadays you sit for forty to eighty minutes in a germ-laden waiting-room packed with people in their Sunday clothes; you and the doctor seem to be the only ones wearing slightly shiny workaday suits. When you eventually get to him you show him your rash.

"Ha!" he says. "A fungus infection. We'll try you with some of this. It is sometimes very effective." You take the prescription to the chemist, and pay him 1*s.*, and he tells you: "This is the very latest from America, and costs the taxpayer 25*s.* a tube."

At the end of a week your rash is still the same; so you go back to the doctor, sit fifty-five minutes in his crowded germ-laden waiting-room, and show it to him again. "Hm!" he says. "We'll try you with this." He scribbles another prescription, muttering as he does so: "This is sometimes very effective indeed." You pay another 1*s.* to the chemist, who tells you: "This is absolutely *the* latest from America, and costs the taxpayer 45*s.*"

At the end of three days the rash has broken out on the other leg and the back of your neck. You also have a cold in the head, which you feel sure you caught in the doctor's waiting-room. However, you go and see him again. "Ah!" he says, peering interestedly at the outbreak on the back of your neck. "You must be allergic to the stuff. A lot of people are, you know." He smiles as if he thinks that ought to amuse you, and scribbles another prescription. "We'll try you with this. It's very soothing." You grab the prescription and hurry out before he has time to tell you that it is sometimes very effective. You take it to the chemist, pay him another 1*s.*, and ask him nervously what it is. "Zinc ointment," he says. "Quite harmless. I always recommend it for skin complaints."

* * *

A man without a smiling face must not open a shop. If that was true in ancient China, it ought to be true in England today; but as a nation of shopkeepers we seem to be in danger of losing our manners. No wonder I feel rebellious and disgruntled, another Angry Old Man: there is more at stake than my cheque for £5. All I wanted was an assortment of stationery. I usually slip into the firm's Manchester shop, see what they have got, and buy what I need: a pleasant personal arrangement with smiles all round. Manchester is an easy run by car or train, and I often go there for other things. But last month I could not spare the time away and Lakeland was deep in snow, so I wrote out a mail-order and posted it to Manchester.

That was where Free Trade died. Without as much as a by-your-leave I was sold like a slave in a slavemarket across the Pennines to the firm's Newcastle branch. No attempt to check that my order could be met over there: in fact it could not. Part deliveries trickled along Hadrian's Wall and down to Lakeland in the next fortnight, with no advice of when the rest would come, or even if it would come at all. Never the most patient soul, I went berserk with the firm's head office in London. After trying to pull a whole lot of wool over my eyes, their Sales Manager firmly insisted that if I chose to be stupid enough to live in the Lake District I must be allocated to the zone of their Newcastle branch for the convenience of the firm and its commercial travellers.

Now Newcastle is a bonny town and I like it very much; but it is a devilish journey to get there over the Pennines, and there are times when we wonder if some people down in London know just where Westmorland is. But we were never conquered by the Normans, and we are damned if we will be allocated and zoned for our shopping. We claim our right to be freemen in a free market, and we shall throw out these repeated attempts, which are becoming all too common nowadays, to tell us where we are to buy the things we want. I had to counter-attack with a threat to return the whole consignment in protest at such terms of doing business before a half-hearted apology could be wrung out of the firm, with a grudging assurance that I could be tolerated in future as a crank with an unnatural desire to shop where it suits me best.

* * *

On following Helen Heardman's advice for the fourth time:

After hectic lunchtime with baby, husband, and two sons aged 4 years and 5 years, see latter off in friend's car, put baby in pram to sleep, face mound of washing up, see harried husband back to wards, do urgent mending, then decide to "relax".

Put pregnant cat in kitchen, fetch textbook, empty bladder as directed, turn two dogs off the sofa, settle down in approved position with sigh of content, start breathing exercises. Congratulate self on muscular control. Baby wakes up. Ignore calls. Breathing exercises no. 2, and—yes no. 3. Can no longer ignore baby's calls. Get him up, cuddle, futile attempt at potting, give him book to play with. Telephone rings.

Exercises for pelvic floor contraction. Settle into position. Baby sits on head. Continue with pelvic rocking. Baby sits on stomach. Telephone rings. Baby yells for attention. Give him scissors and fountain-pen to play with!

Exercise for posture correction. Baby spills bottle of milk and breaks glass. Exercise for cleaning floor on hands and knees.

Finally, relaxation. Study requirements: (*a*) Full support of all parts of the body—correct; (*b*) No muscle tension—all right; (*c*) Peace of mind. Give up.

Look at clock. Time to fetch boys from school.

* * *

The *New York Times*, besides all the news that's fit to print, has lately published a large advertisement for insectivorous plants. Perhaps this is because the delinquent scientists have not yet invented an electrical bug-catcher. If so, it must be the only electrical gadget waiting to be invented. Besides such obvious things as electric dish-washers and seats to carry you up the stairs in your house, you can now buy electric shoe-polishers, can-openers, manicure kits, and even pencil-sharpeners. Where will it all end? Perhaps in the box devised by a distinguished engineer of the Bell Telephone Company: this box, it is said, has no function, but if you open it a hand comes out and shuts it.

Letters to the Editor

LEGAL ASPECTS OF HOMOGRAFTING

SIR,—Homografts have already an important place in surgery. For example, skin homografts, despite the fact that they are destroyed within a week or two, may be life-saving in severely burned patients, and on the other side of the Atlantic a whole kidney has been successfully transplanted from an identical twin donor on more than a dozen occasions. There are now moreover good grounds for believing that methods will be found of making homo-transplants of tissues in general survive permanently in man. Progress has also been made in the development of methods of storing tissues and cells in a viable state, though the long-term storage of whole organs is still not possible.

Even if the immunological barrier to homograft survival can be removed or surmounted, however, and methods of storing whole kidneys and other organs for days or weeks become available, patients will not reap the full benefit of these discoveries until the legal position regarding homografting has been clarified.

The Corneal Grafting Act of 1952 regularises the removal from cadavers, under appropriate conditions, of eyes to provide corneal grafts. In New Zealand the Medical Amendment Act of 1954 makes similar provision in respect of all other tissues and organs, but, except as a shining example of enlightened legislation, this is of no help to patients in the United Kingdom. In Edinburgh, for example, I have been instructed by my hospital board to refrain from establishing a skin bank on the lines of the one I operated in New Zealand, on the grounds that the law does not permit the removal of skin after death for the purpose of grafting. Admittedly one hears from time to time of local arrangements with various authorities whereby the removal of arteries, and on occasions skin, from a cadaver is undertaken provided that the relatives' consent is given, but this is surely not an adequate way of dealing with the problem.

If legislation is to be introduced it is to be hoped that special consideration will be given to the fact that, whereas satisfactory corneal grafts may be obtained from eyes removed several hours after death, organs such as the kidney must be removed within a matter of minutes if they are to be of any use.

It would seem desirable also that legal provision should be made for the removal of tissues, including the removal of one kidney, from living healthy donors who wish to provide a lifesaving graft for a particular patient. At the moment the clearest indication for a voluntary donation of this kind is the desperate need of a kidney by a patient who is lucky enough to have a healthy identical twin, but current work on the use of irradiation and cytotoxic drugs to facilitate homograft survival encourages the view that the range of usefulness of kidney transplants will increase, perhaps very soon.

It is clearly desirable that both doctors and laymen should have a proper appreciation of this situation. It is surely also desirable that some sort of working party should be set up to study the problem from a medicolegal point of view, and, one would hope, advise the Government on appropriate legislative action.

Department of Surgical Science, University of Edinburgh. M. F. A. WOODRUFF.

FLUORIDATION

SIR,—Dr. Dobbs (April 2) rather suggests that because your survey dealt mainly with dental caries in children, it left much to be desired. Is not the only reason for most of us being interested in fluoridation that it offers a hope of reducing dental caries to manageable proportions? In this area, before fluoridation, only 2 of every 100 children aged 14 were free from dental disease. I have reason to believe that in many parts of the country the position was no better. For years, the orthodox advice of a good mixed diet, limitation in the consumption of refined sugar, and regular cleaning of the teeth has completely failed to result in any noticeable reduction in dental caries. It is as a result of these facts that many in the Public Health Service feel bound to pay the greatest regard to any substance which can improve this deplorable state of affairs.

If Dr. Dobbs is prepared to agree, and having had a scientific education, he can scarcely fail to do so, that the effect of the fluoridation of public water-supplies by man is similar to the effect of drinking water which is naturally fluoridated, then surely it is passing strange that in those parts of the country where adjacent villages have water with high and low fluoride levels naturally, the general practitioners practising there have not so far reported any ill effects associated with fluoride. This is, of course, a test of clinical judgment, in which Dr. Dobbs does not believe. I, on the other hand, have seen sufficient of my brethren in general and consulting practice to have considerable confidence in their diagnostic ability.

In this area, fluoridation has been in operation for four years and so far no ill effects attributable to it have been reported to me by any local doctor.

It appears then that Dr. Dobbs does not think much of the clinical judgment of the profession. Nor does he place much value in the statistical work of considerable magnitude that has been carried out on the subject. He believes that the detection of the alleged risks of fluoridation will prove so difficult as to make it doubtful if they will be recognised at all.

Bearing in mind the good effects on the teeth which will result from fluoridation and the great amount of research and experience which have accrued over the years, it would not seem reasonable to withhold these beneficial effects, especially from the children (who cannot write letters on their own behalf) because Dr. Dobbs and those who think like him believe, or would have us believe, that certain ill effects which they cannot specify may *possibly* affect *someone* at *some* future date.

Health Department, Kilmarnock. BRYCE R. NISBET Medical Officer of Health.

SIR,—As a dental surgeon in general dental practice I would be delighted if some specific such as fluoridation could reduce dental caries. Despite the figures produced by many investigators we do not know if fluoridation is absolutely safe to everybody over a period of years. Who can really say that an illness occurring in a patient drinking fluoridated water would have still overtaken him had he not been drinking the water?

Does the condition justify the means? Let us face it. Teeth are quite unnecessary to survival in our civilisation. Their preservation is certainly æsthetically desirable, but that as a reason is simply not good enough to justify adding to water a substance which may be toxic to some. If dental decay was a killing disease the case for enforced medication of the entire population could be argued. In the present state of knowledge it is not a killer and in the present state of knowledge fluoridation is not absolutely known to be safe. I think, sir, that it would be a sad day for us all when in the case of a disease of inconvenience we forgot our responsibility to the tiny minority.

Salisbury. HUGH V. CAPSTICK.

FLUORIDATION AND GASTRIC CANCER

SIR,—In a letter in your issue of March 26 Dr. Burrowes suggests, by a comparison which he made of deaths in the small towns of Donington and Crowland over a period of ten years, that there may be a relationship between the consumption of naturally fluoridated water and carcinoma of the stomach.

During the period 1952–58 inclusive the number of deaths registered as due to this cause in Donington (population 1917) was 4, average age at death 61 years; in Crowland (population 2833) 12 deaths, average age at death 68·5 years; figures for a 10-year period are not available. It will no doubt be agreed that these towns are too small to provide reliable comparative statistics; any deduction therefrom could only be regarded as trustworthy in proportion as the observations were numerous, and on the assumption that the latter were at the same time accurate and comparable.

The public water-supplies in Donington (from West Pinchbeck) and Spalding (from Bourne) are derived from bores in the counties of Holland and Kesteven respectively, the average concentration of fluorine being for the former 0·5 p.p.m. and 0·1 p.p.m. at Spalding. Dr. Burrowes gave the latter value as 0·5 p.p.m. A bore at Deeping St. Nicholas supplies water with a concentration of 2·9 p.p.m. F to Crowland: this supply came into use about a year ago; the earlier supply from Deeping, according to recent information, contained 3 p.p.m. F. As a matter of interest, it is also necessary to take into account the fact that there are indigenous private bores, more common in South Kesteven than in the southern part of the County of Holland, which provide higher concentrations of fluorine. This is due to the occurrence of fluorine contours which run in the direction north to south in the extreme south-east of Kesteven and in the south-west of Holland The concentration of fluorine gradually rises from a mere trace in Kesteven to around 4·5 p.p.m. in Spalding and Crowland in the east.

Local statistics do not appear to support any suggestion that there is a causal relationship between the consumption of naturally fluoridated water and the incidence of carcinoma of the stomach in the natural fluoride areas of South Kesteven Rural District (population 14,394) and Spalding Rural District (population 18,890). The average death-rate from carcinoma of the stomach in the former rural district during the years 1944–58 was 0·29 per 1000 of the population, as compared with an average death-rate of 0·29 per 1000 for the same period for the remainder of the County of Kesteven (population 133,500) which has no naturally fluoridated water in the public water-supplies. A similar comparison has been made in the County of Holland; in the Rural District of Spalding, which includes the towns of Donington and Crowland, the average death-rate from carcinoma of the stomach during the years 1952–58 was 0·35 per 1000 of the population, as compared with 0·32 for the remainder of the County of Holland (population 102,600).

During the years 1947–53, the average death-rate for carcinoma of the stomach in England and Wales was 0·33 per 1000 of the population.

During the past six years several papers have been published upon various aspects of fluoridation in South Lincolnshire, and these [1–5] may be of interest.

J. H. CHALMERS CLARKE
County Medical Officer of Health.
Sleaford, Lincs.

SNAKEBITE

SIR,—Dr. Penman (April 2) is to be congratulated on his attempt to preserve our language from further debasement through pseudoscientific jargon. While the ugly word, "envenomation", occurs in Webster's New International Dictionary—a most conservative and valuable American work—it is not included in Webster's New Collegiate Dictionary, and, fortunately, cannot therefore be assumed to be of common usage in the United States. The equally objectionable French word, *envenimement* (which is to be found even in the Petit Larousse), is, to the best of my knowledge, never used by French writers. Let us, by all means, be satisfied with "poisoning" and *empoisonnement*.

Bransgore, Hampshire. R. H. AHRENFELDT.

1. Chalmers Clarke, J. H. *Med. Offr*, 1954, **92**, 39.
2. Chalmers Clarke, J. H. *J. Brit. Waterwks Ass.* 1954, **36**, 497.
3. Chalmers Clarke, J. H. *ibid.* 1955, **37**, 664.
4. Lamont, P. *ibid.* 1959, **41**, 68.
5. Chalmers Clarke, J. H., Mann, J. E. *Brit. dent. J.* 1960, **108**, 181.

MATERNAL AGE IN MONGOLISM

SIR,—In presenting an instance where trisomy 22 has not been found in a patient with mongolism, Dr. Polani and his colleagues (April 2) lay great emphasis on the youth of the patient's mother at the time of the affected birth. In support of their view that mongolism in births to young mothers may be ætiologically distinct from the condition in offspring of older mothers, they quote assertions by Penrose [1 2] that maternal age at birth of mongols is bimodally distributed and that mean maternal age is low in cases where a maternal relative is also affected.

But there is nothing remarkable in the finding that a mother of a mongol is young. Although the risk of any birth being affected rises sharply with advancing maternal age, the large number of births occurring in the general population at the younger maternal ages results in a proportion of mongols being born to young mothers.

In a series [3] of 241 mongols born in Birmingham, 20 (8%) were born to mothers under 25 years of age and 57 (24%) were born to mothers under 30 years of age at the time of the birth. Thus, although mongolism is rare among births to young mothers, young women are by no means rare among the mothers of mongols.

The hypothesis of Penrose that the distribution by maternal age at birth of mongols may represent the superimposition of two distributions relating to ætiologically distinct groups of cases, depends largely on a demonstration of bitangentiality in the maternal age-distribution of a series of cases assembled from the literature. It is important to consider alternative explanations of Penrose's finding.

(1) Since a series assembled from the literature is heterogeneous in respect of the populations of births from which cases are drawn, its maternal age-distribution may reflect differences between these populations in maternal age-distributions for all births. Distributions by maternal age for unaffected births exhibit secular and regional variation.

(2) The cases in Penrose's series were largely ascertained at some time after their birth and thus are survivors from an unidentifiable population of affected births. Since early mortality in mongols is high and related to maternal age at birth, the maternal age-distribution for such a series of survivors may most imperfectly resemble that at birth. It is of interest that the series published by Carter and MacCarthy [4] and drawn from consecutive maternity-hospital births exhibits no significant bitangentiality of its maternal age-distribution.

(3) Even if the preceding explanations are rejected, an observation that maternal age at birth of mongols is bitangentially distributed is hardly surprising since the distribution is the product of the maternal age-distribution for the general population of births and the maternal age-distribution of the risk that a birth is affected. Maternal age at birth for the general population is distributed around a single mode occurring in the 25–29 age quinquennium. The maternal age-distribution of the risk that a birth is affected may be examined by considering maternal age-specific incidence in a series of

1. Penrose, L. S. *J. ment. Sci.* 1951, **97**, 738.
2. Penrose, L. S. *Ann. N. T. Acad. Sci.* 1954, **57**, 494.
3. Smith, A., Record, R. G. *Brit. J. prev. soc. Med.* 1955, **9**, 51.
4. Carter, C., MacCarthy, D. *Brit. J. soc. Med.* 1951, **5**, 83.

TABLE I—INCIDENCE OF MONGOLISM ACCORDING TO MATERNAL AGE AT BIRTH
(Data from Carter and MacCarthy [4])

Maternal age Years / Group x	15–19 1	20–24 2	25–29 3	30–34 4	35–49 5	40–44 6	45+ 7
No. of cases	0	5	6	25	29	31	4
Incidence per 100,000 births	0	28	29	172	352	1418	2632
d_x	..	−27	+142	+137	+886	+148	..

$d_x = n_{x-1} - 2n_x + n_{x+1}$ where n_x is the number of affected in 100,000 births at maternal age quinquennium x.

consecutive births. Suitable data have been published by Carter and MacCarthy [4] and the distribution of incidences from their series (table I) exhibits no evidence of bitangentiality. The value d_x ($=n_{x-1} - 2n_x + n_{x+1}$ where n_x is the number of affected in 100,000 births at the maternal age quinquennium x) provides a simple indication of bitangentiality since it has positive values where the distribution curve is convex downwards and negative values where it is convex upwards, so that single negative values surrounded by positive values represent points of upward convexity in an otherwise upwardly concave curve.[5]

Dr. Polani and his colleagues also quote other evidence published by Penrose [2] that mean maternal age is lower for affected births where there is an affected maternal relative than it is where a paternal relative or no relative is affected. Penrose found this lowering most marked where the affected relatives were sibs of the parents of propositi. However the data on which these comparisons were based were not numerous, and further data [6] do not support Penrose's finding. In the Birmingham series previously referred to, mothers of 217 cases were interviewed and information was recorded on inter alia the existence of affected relatives. 6 affected parental sibs were reported. Table II shows data on these cases together with those of Penrose, according to whether a maternal or a paternal sib was affected. The difference between the mean maternal ages is not significant. In any case, where numbers are so small the mean leaves much to be desired as a summarising index; inspection of the distributions themselves is more informative. These do not seem essentially different either from each other or from distributions for patients in whom no relatives are affected.

TABLE II—MATERNAL AGE OF MONGOLS HAVING AFFECTED AUNTS AND UNCLES

Maternal side affected		Paternal side affected	
Maternal age (yr.)	Source of case	Maternal age (yr.)	Source of case
18	Smith [6]	23	Penrose [1]
19	Penrose [1]	30	Smith [6]
22	Penrose [1]	31	Penrose [1]
32	Smith [6]	34	Penrose [1]
34	Penrose [1]	35	Penrose [1]
36	Smith [6]	38	Penrose [1]
37	Smith [6]	40	Penrose [1]
37	Penrose [1]	45	Penrose [1]
38	Smith [6]		
39	Penrose [1]		
Mean 31·2		Mean 34·5	

Difference between means = 3·3 ± 3·3 years.

Although the motive for examination of the reported patient is stated to be a belief that low maternal age may be a distinguishing characteristic of an ætiologically distinct category of affected, the finding of an unusual karyotype in one case born to a young mother cannot be regarded as endorsing the validity of the belief. Fortunately the interest of the report in no way depends on the credentials of the hypothesis that prompted it. Together with the report by Dr. Fraccaro and his colleagues in the same issue, it provides evidence that mongolism may arise from other anomalies of pair number 22 (21 in Fraccaro's system) than trisomy.

Department of Public Health and Social Medicine, Queen's College, Dundee. ALWYN SMITH.

5. Haldane, J. B. S. *Ann. Eugen.* 1951, **16**, 359.
6. Smith, A. Mongolism; an Ætiological Study. Ph.D. thesis, University of Birmingham, 1955.

"CRISIS IN NURSING"

SIR,—The General Nursing Council is attempting, with the best of intentions, to raise the standard of nursing training, but the course recommended seems calculated to produce what must be in effect sub-standard doctors rather than the well-trained nurse so rightly sought after by Mr. Robb (March 26). Surely art is equally if not more important than science in the management of the patient—a consideration that seems to be forgotten by the G.N.C. in its attempts to keep up with the medical Joneses.

The laudable attempts of the G.N.C. to streamline training by cutting out teaching for the special diplomas should not mean, however, a replacement by ever-increasing cramming with each new fashionable "ism".

With regard to present staffing problems, it might be more logical to accept trainees to a particular H.M.C. group rather than to an individual hospital as at present. The major experience would be gained at the main general hospital, but it must surely be to the mutual advantage of all to make use of the powers of secondment implicit in such an arrangement.

Chadwell Heath Hospital, Romford, Essex. I. M. LIBRACH.

IMMUNE TOLERANCE IN MOTHER AND FŒTUS

SIR,—In his letter of Feb. 27, Dr. Michael Galton makes the novel suggestion that the nuclei of syncytiotrophoblast may be haploid. His view is based in part on an apparent misinterpretation of Sohval et al.[1] Thus he writes:

"Recently, careful search by Sohval and his colleagues has failed to demonstrate the presence of the Barr nuclear chromatin body in the nuclei of these cells (i.e., the syncytiotrophoblast) in the placentas of female fœtuses, although it has been identified in every other cell type of such placentas."

They wrote:

"The nuclei least satisfactory for identification of sex chromatin were those of the syncytiotrophoblast. In fact, excessive and coarse chromatin granulation made it virtually impossible to ascertain the presence or absence of sex chromatin in these nuclei."

This granularity of the syncytial nuclei is an old annoyance to those interested in the sex particle but, clearly, technical difficulty in demonstrating the particle is not of itself a reason for doubting its existence. The practical problem is, of course, to decide which of a number of very eligible particles, on morphological grounds, is in fact the sex chromatin, and in the full-term placenta this can rarely be done with any certainty. However, in young placental tissue, up to about the 10th week, there can be seen in occasional syncytiotrophoblastic nuclei in female conceptuses a mass of chromatin morphologically identical with the sex particle. Suitably non-granular or "transparent" nuclei are scanty even here (and have to be distinguished with care from the nuclei of poorly preserved cytotrophoblast) but they can be found.[2] Similarly in hydatidiform moles, scanty non-granular nuclei occur in the syncytiotrophoblast, and in such nuclei an apparent sex particle can also be found, as may be seen in an illustration published three years ago.[3]

The difference of the chromatin pattern of the nuclei in the syncytiotrophoblast and in the cytotrophoblast is so marked

1. Sohval, A. R., Gaines, J. A., Strauss, L. *Ann. N.Y. Acad. Sci.* 1959, **75**, 905.
2. Park, W. W. *J. Anat.* 1957, **91**, 369.
3. Park, W. W. *J. Path. Bact.* 1957, **74**, 197.

that it might well indicate a chromosomal difference of some kind, but this cannot be haploidy of every nucleus in the syncytial form. That a majority of syncytial nuclei are haploid is, of course, possible, as Dr. Galton suggests, but it would not be right to ignore his distortion of Sohval et al.; further, as it stands, it is in contradiction with facts as I have found them.[2 3] It is also inaccurate of Dr. Galton to say that no account has been taken of the antigenic action of the placenta; this was done in 1959.[4]

Department of Pathology,
Queen's College,
University of St. Andrews,
Dundee.

W. W. PARK.

INFANTILE STRUCTURAL SCOLIOSIS

SIR,—Whilst in no way wishing to be " stirred " into controversy by Mr. Denis Browne's letter of March 26, I believe it important to consider a number of his points.

It became apparent from studying infants with structural scoliosis of unknown ætiology that there were two groups, resolving and progressive. The former, of which there have been 77, had a structural scoliosis which completely disappeared without treatment. There seems little point therefore in applying splintage. 60–70% of infants with such structural curves belong to this group.

The progressive variety, usually (but not invariably) easily distinguished from the resolving, has not, in my experience, responded satisfactorily to any form of treatment, applied early or late. Mr. Denis Browne is incorrect in suggesting that we do not treat these children, but having abstracted those undergoing natural resolution, optimism concerning the effects of treatment is not substantiated by the results.

Having seen well over 2000 patients in ten years I do not believe that " it is very rare ". Mr. Denis Browne suggests it is due to malposition in utero, as it may well be. However, in the whole series only 6 were noticed at birth and many not until the second or even third year. The progressive curves in these infants are in no way distinguishable from the typical idiopathic curves of the second decade. I think it erroneous to blame the intrauterine position for idiopathic curves in infants and ascribe a different cause to those occurring later.

The Royal Infirmary,
Edinburgh.

J. I. P. JAMES.

LINOLEIC ACID IN THE CHOLESTEROL ESTERS OF THE AORTIC WALL

SIR,—In a paper in your columns in 1958 we reported [5] that the percentage of saturated fatty acids in the cholesterol esters of the aortic wall decreases with increasing severity of atherosclerosis. Since then we have extended our analyses of the lipids of the arterial wall and the results will be published soon. One of the conclusions we can now draw with certainty is that the linoleic-acid percentage in the cholesterol-ester fatty acids (C.E.F.A.) increases considerably with atherosclerosis. Our present mean values (determined by gas chromatography) are 24·5% for undiseased aortas and 37% for aortas with atheromas and/or plaques.

Sinclair [6] mentioned " a chemical error that has been made in your columns on various occasions by distinguished fat chemists ". He pointed out that it has mistakenly been taken for granted that the octadecadienoic acid detected by gas chromatography is identical with linoleic acid, whereas it could equally well be a structural isomer of it. We have now established by ozonolysis and oxidation, followed by identification of the degradation products, that the double bonds of our octadecadienoic acid (isolated from the C.E.F.A. of atheromatous aortas by preparative gas chromatography) are in the same positions as in linoleic acid; infra-red analysis of the same sample (for which we are indebted to the Unilever Research Laboratory, Vlaardingen, Holland) led to the conclusion that more than 98% of these bonds are *cis*-orientated. This proves that the octadecadienoic acid isolated from the cholesterol esters of the aortic wall is identical with linoleic acid.

In the C.E.F.A. saturated acids (the mean total percentage of which decreases from 31 to 17%), the largest percentage decrease, relative to the value in undiseased aorta, is found for stearic acid. Since the two most striking changes in the C.E.F.A. are the increase of linoleic acid and the decrease of stearic acid, I would propose the ratio of linoleic acid to stearic acid as an index of the degree of atherosclerosis as reflected by the C.E.F.A. This index increased, in the preparations we have examined, from values between 2 and 7 for undiseased aortas to values between 15 and 35 for aortas with severe atherosclerosis.

Physical Chemistry Laboratory,
University of Leiden,
Netherlands.

C. J. F. BÖTTCHER.

SERUM-LIPID STUDIES AND NICOTINIC-ACID THERAPY

SIR,—For the past twelve months we have been using large doses of nicotinic acid (3–6 g. daily) in the treatment of patients with ischæmic heart-disease. Only patients with some clear abnormality of their blood-lipids have been included in our group of 25. We can confirm the favourable reports of Altschul et al.[1] and Galbraith et al.[2] and of other workers. With few exceptions patients have shown a reversal towards the normal lipid pattern.

All the disorders were initially detected through a routine blood-lipid study. We can confirm that the side-effects of nicotinic acid have been transient and unimportant and are not a serious drawback to treatment. We (like others) have not noted any general development of tolerance to the drug, although twelve months cannot be considered a sufficient length of time to form any definite view on this point.

Included in a full lipid study we do a routine lipid-tolerance test. We have confirmed that many patients with ischæmic heart-disease show an abnormal rise in total blood-lipids after the ingestion of 75 g. fat and that this reduced tolerance may be greatly improved following administration of nicotinic acid in large doses. This is in line with the work of Pomeranze et al.[3] who described an excessive and prolonged rise in total fat acids after a standard fatty meal in patients with arterial disease. They observed some improvement of fat tolerance in these patients when they were kept on a low fat intake.

Our standard lipid-tolerance test is performed as follows:

A specimen of blood is taken from the fasting patient. 75 g. of a synthetic fatty preparation (' Prosparol ", Duncan, Flockhart) is then administered in a chocolate drink and further specimens of blood are taken at intervals of 2 and 4 hours. The patient is kept at rest before and during the test. Each specimen is examined for total lipids by Kunkel's method [4]; the fasting specimen is also examined for total protein, lipoprotein pattern, and total serum-cholesterol. All specimens are examined for optical density, and a clearing test is performed after 4 hours by the intravenous injection of 300 units heparin, the final specimen being taken 15 minutes later.

In young healthy adults the lipid rise is rarely more than 100 mg. and never more than 150 mg. per 100 ml. In some patients the rise has been in excess of 150 mg. and has been as high as 600 mg. per 100 ml. This abnormally high rise appears to bear no close relation to the fasting total-lipid or serum-cholesterol levels.

An abnormal lipid-tolerance test and/or deficient clearing may be the only unusual findings in this lipid study. We have not sufficient experience as yet to correlate lowered fat tolerance or deficient clearing with other abnormalities in blood-lipid behaviour; if indeed such a correlation exists at all. We would, however, suggest that a lipid-tolerance test might be useful in studies of patients suffering from coronary or peripheral

4. Park, W. W. *Ann. N.Y. Acad. Sci.* 1959, **80**, 152.
5. Böttcher, C. J. F., Keppler, J. G., ter Haar Romeny-Watchter, C. C., Boelsma-van Houte, E., van Gent, C. M. *Lancet*, 1958, ii, 1207.
6. Sinclair, H. M. *ibid.* 1959, ii, 789.

1. Altschul, R., Hoffer, A., Stephen, J. D. *Arch. biochem. biophys.* 1955 **54**, 588.
2. Galbraith, R. A., Perry, W. F., Beamish, R. C. *Lancet*, 1959, i, 222.
3. Pomeranze, J., Beinfield, W. H., Chessin, M. *Circulation*, 1954, **10**, 742.
4. Kunkel, H. G., Ahrens, E. H. Transactions of 7th Liver Injury Conference of Josiah Macy, Jr., Foundation. January, 1948.

vascular disease. Obviously a number of factors, such as completeness of fat absorption, metabolism or deposition, must be considered in interpreting lipid-tolerance tests. The improvement in fat tolerance in some of our patients with coronary disease on nicotinic-acid therapy prompts us to report our impressions at this stage.

Two of us (J. J. F. and A. H.) are grateful to the Medical Research Council of Ireland for grants, and to the British Drug Houses Ltd. for some supplies of the special 0·5 g. tablets of nicotinic acid used. We are obliged to R. McFarlane for technical assistance.

O. FITZGERALD
R. MULCAHY
J. J. FENNELLY
A. HEFFERNAN.

St. Vincent's Hospital, Dublin, and University College, Dublin.

ELECTROCARDIOGRAPHY AND HYPERKALÆMIA

SIR,—I read with interest the article about the clinical course of uncomplicated acute tubular necrosis by Dr. Loughridge and others (Feb. 13) in which they state that electrocardiographic evidence of hyperkalæmia is an indication for hæmodialysis.

I have seen 10 patients in this hospital with severe uræmia, oliguria, and anuria due to various causes. All of them had high blood-urea, blood-nitrogen, and blood-creatinine, and elevated plasma-potassium. Only 3 patients had electrocardiographic evidence of hyperkalæmia, such as tall peaked T waves and arrhythmia. 2 patients had equivocal changes. The rest did not show any E.C.G. evidence of hyperkalæmia, although the plasma-potassium values were above 7 mEq. per litre. *No* T-wave changes, conduction defects, disappearance of P waves, bradycardia, arrhythmia, or ventricular tachycardia were noticed in these patients.

I should like to add that the E.C.G. is a poor indication of the degree of hyperkalæmia. Sometimes we can see changes with a plasma-potassium of less than 6·5 mEq. per litre, and at other times we can see E.C.G. changes only if the potassium is above 7 mEq. per litre.

Elevation of the plasma-potassium is a better indication for hæmodialysis than E.C.G. evidence of hyperkalæmia.

New York City. P. NARASIMHAN.

THE PSYCHOTHERAPIST AS ARTIST

SIR,—Dr. McConaghy (March 19, p. 641) mentions the confusion that can be created in the mind of the patient by non-directive psychotherapists. But I think that just as impressive a confusion can be created in the mind of the therapist by the patient. One feels that no matter what sort of psychiatrist it is, the more confusion he is in, the more he may tend to act aggressively towards the patient with regard to treatment. Bearing that in mind, I should like to amplify some of Dr. McConaghy's remarks.

Psychotherapy is not primarily a scientific discipline, but an artistic activity that involves the creative powers of both the therapist and the patient. It is not, by analogy, painting by numbers. The latter may be enough or necessary initially—the form of directive psychotherapy. Once the patient expresses dissatisfaction by not getting better, he is probably ready to use his own creative feelings, as yet untapped.

Here it is that the therapist as an artist becomes involved in creating, with the patient, the evolution of the latter as a mature human being. He does this by enabling the patient to become aware of his feelings and of his ability to create with them a more satisfactory relationship for himself.

Susanne Langer states that what is artistically good is whatever articulates and presents feeling to our understanding. This is precisely what psychotherapy is about.

Although our material is human, we also feel involved in its creation. Not only is it in our image, but the patient also has the ability to use the creativity that he finds in himself. This proclaims his unique being—to be judged not as a cure but by his value as a human being (that is, not in scientific terms only, but also in artistic ones).

London, W.5. F. J. LICHTIGFELD.

ROLE OF POTASSIUM IN MALIGNANT DISEASE

SIR,—It has long been known that potassium plays some part in the metabolism and growth of tumours. An average estimate of the potassium content of benign tumours has been given as 1·4% of tumour weight, and that of malignant tumours as 2·3%.[1] In 1946 Brunschwig [2] recorded a series of gastric carcinomas that were analysed for potassium content, and compared the results with similar analyses of gastric mucosa from patients with no carcinoma. The average potassium content for the former was 292·4 mg. per 100 g. of tumour, and for the latter 217·5 mg. per 100 ml. Similar studies were carried out for carcinomas of the colon and adjacent mucosa. The increase in potassium content of the carcinomas relative to the mucosa was rather striking,[3] the average for the carcinoma being 317 mg. per 100 ml., and for the uninvolved mucosa 192 mg. per 100 ml. More recently attention has been drawn to potassium-secreting tumours by Roy and Ellis.[4] There therefore seems to be little doubt that with few exceptions the potassium content of malignant neoplasms is higher than a similar weight of normal tissue.

The amount of potassium in the adult body is of the order of 150–200 g. Of this amount, 3 g. is in the extracellular fluid, so that the remaining great bulk of body-potassium is intracellular and intranuclear—i.e., over 95%. There are three naturally occurring isotopes of potassium, ^{39}K, ^{40}K, ^{41}K, with an abundance of 93·08%, 0·0119%, and 6·91% respectively. ^{39}K and ^{41}K are stable, but ^{40}K is a radioactive isotope, present therefore to the extent of 12 parts in 100,000 of the ordinary mineral potassium, and possessing a half-life of $1·3 \times 10^9$ years. In spite of this very long half-life, the emitted rays possess considerable energy, 1·4 meV beta radiation, and a very hard gamma radiation 1·5 meV, to the extent of about one-tenth of the total.

^{40}K is the principal natural source of radioactivity in the human body, and life as such has evolved in the presence of this small radiation, though it has been established that this radiation is not essential to life.[6] Could, however, this radiation ever be harmful? Certainly not under the average concentration of ^{40}K within the cell. The dose is extremely minute and the span of human life far too short for any observable effect of this very low-intensity radiation. The question, however, would be open for argument if it could be proved that this average concentration in the cell was, in fact, subject to fluctuation. That this is so is shown by an analysis of the body-potassium in 10 subjects. The total potassium content of the body, calculated as a percentage of body-weight, varied from 0·17 to 0·24.[7] Though the kidneys are very efficient in sweeping out excess potassium, there is a time-lag in this excretion, and therefore a continuous high intake of potassium necessarily implies a continuous high intracellular content of this cation.

It may be presumed that any excess intracellular content is of no special significance bearing in mind the extremely minute dosage of this low-intensity radiation; what, however, if it could be further proved that the ratio of the radioactive isotope to the stable isotope was variable? This fact could then indeed be very pertinent. Investigations have disclosed the somewhat surprising fact that the abundance ratio of the isotopes of potassium is not a constant figure for all organic

1. Kovacs, L., Ambrus, M. *Magyar Orv. Arch.* 1931, **32**, 220.
2. Brunschwig, A., Dunham, L., Nichols, S. *Cancer Res.* 1946, **6**, 230.
3. Dunham, L., Nichols, S., Brunschwig, A. *ibid.* p. 233.
4. Roy, A. D., Ellis, H. *Lancet*, 1959, i, 759.
5. Rankama, K. Isotope Geology; p. 302. London, 1954.
6. Vinogradov, A. P. *Nature, Lond.* 1957, **179**, 308.
7. Rundo, J., Sagild, V. *ibid.* 1955, **175**, 774.

tissue. In other words, fractionation of isotopes is a proven fact in Nature.[8] Lasnitzki and Brewer carried out an analysis of potassium in human cancer, and found that the isotopic ratio $^{39}K/^{41}K$ of potassium in tumours showed, if compared with that of mineral potassium, a slight but definite increase, thus indicating a corresponding decrease in the percentage of the heavy isotope ^{41}K. In an analysis of the potassium content in eleven cases of human cancer, the average percentage of ^{41}K was 6·5 (normal 6·9), the average isotopic ratio $^{39}K/^{41}K$ being 14·3 (normal 13·5). Since a deviation of this kind could not be observed with potassium in any of the normal tissues, it appeared that the isotopic constitution of potassium in normal tissues and tumours was appreciably different.[9] In addition, it has been found that the potassium content of muscle from tumour-bearing animals, compared with the potassium in muscle from normal animals, showed a deviation similar to that observed with potassium in tumours,[10] a finding of possible significance.

In other words, fractionation of the isotopes of potassium by the renal tubules or cell membranes is a physiological possibility, and in cases of cancer it seems that there is a selective affinity for the lighter isotopes, including ^{40}K. The body is therefore carrying out a process akin to the electromagnetic separation of isotopes as carried out in the laboratory, and there is no reason to suppose that ^{40}K as well as ^{39}K would not be fractionated in the same way. There are therefore two separate factors for consideration; the first, that the intracellular content of potassium can be permanently in excess of body requirements, and that this would carry with it an increase in the minute intracellular radioactive content; the second, that this minute intracellular radioactive content may be further stepped up by a physiological fractionation of ^{40}K.

One might expect that tissues containing a large amount of potassium would be more liable to undergo malignant change. This is not necessarily true, since cancer-prone cells are those that undergo frequent mitosis, as for example the cells of the respiratory, alimentary, and endocrine systems. Mitosis is rare in muscle tissue, and so are neoplasms. It is true, however, that individuals on a high-potassium diet appear to be more liable to develop cancer. This association is firmly supported by circumstantial evidence.

The incidence of tumours in animals is greater when they are fed on a liberal diet compared with those fed on an adequate but low-calorie diet, and it is also clear that there is a relationship between national income and diet, and national income and cancer. The higher the annual budget per head of population, the greater the incidence of diagnosed cancer, and this seems to be associated with the fact that the higher the income of the country the greater the amount of food consumed.[11] Further, the consumption of protein and fat increases with the income of the country, and it is these foods that are high in potassium content.

The biological effects of high-intensity radiation are well known, but little or nothing has yet been learnt about the effects of low-intensity radiation on the human body. This is partly accounted for by the fact that most experimental animals are unsuitable owing to their short span of life; in other words, these animals would die in the natural course of events before any effects of this low-intensity radiation became apparent. This extremely minute radiation is undoubtedly increased by the storage of large amounts of potassium—e.g., many times the amount required to carry out all normal physiological functions. How much more could this minute radiation be increased as the result of the selective affinity of the renal tubules or cell membranes for the lighter isotopes ^{39}K and the radioactive ^{40}K? And how significant could this be when it is realised that this radiation is both intracellular and intranuclear—in other words, placed at the fountain head of mitosis.

It is not suggested that potassium is a causative factor in all cancers; indeed, the number of known carcinogens increases daily, each one more powerful than its predecessor. What I put forward for expert thought, however, is a hypothesis that potassium could be an initiating factor in the onset of an ordinary non-industrial type of cancer.

London, W.1. DESMOND K. MULVANY.

8. Rankama, K. Isotope Geology; p. 147. London, 1954.
9. Lasnitzki, A., Brewer, A. K. *Cancer Res.* 1941, **1**, 776.
10. Lasnitzki, A., Brewer, A. K. *ibid.* 1942, **2**, 494.
11. Data compiled from Food Balance Sheets (Food and Agriculture Organisation, Rome, 1955) and from Statistics of National Income and Expenditure (Statistical Office, United Nations, New York, 1955).

A NEW FILM

SIR,—May I make a brief comment on your very fair review of April 2 (p. 777) of the film *They Breathe Again?*

The film is intended primarily for nurses, as well as for medical men who may never work in a respiratory unit, but may find useful a clear statement of the whys and wherefors in dealing with the types of poliomyelitis most dangerous to life. For this reason the question of biochemical control and the regulation of pulmonary ventilation were deliberately omitted, and these two subjects would seem to merit the production of a separate film.

The Dräger meter was used because of the larger size and clarity of the dial.

I should add that the film can be borrowed from the hospital free of charge.

Rush Green Hospital,
Romford,
Essex. E. JAMES.

PLACENTA PRÆVIA

SIR,—Certain points that arise from Professor Macafee's reply (April 2) need further discussion.

(1) It is not merely the "occasional case" of antepartum hæmorrhage in which there is doubt about the cause of bleeding. In practice the problem is arising continually. Major placenta prævia usually causes no diagnostic problem but rather the lesser ones in which bleeding can still be dangerous.

Displacement of the presenting part as a sign of placenta prævia is used alike in clinical and radiological examination; yet the difficulty of relying on clinical examination alone in many cases is shown by the fact that even when there are both antepartum hæmorrhage *and* a high head, there will be found just as many cases without as with placenta prævia. For instance, in our series only 13 out of 50 cases of placenta prævia showed significant displacement of the presenting part along with bleeding; yet out of 84 other patients who bled and subsequently were proved not to have placenta prævia no less than 25 were found to have a high head.

That is the diagnostic problem which we feel can best be solved in selected cases by placentography, avoiding dangerous complacency on the one hand and overanxious conservatism on the other.

(2) Professor Macafee has stressed the placenta prævia that has already begun to bleed. Surely it is even better to teach our students and still more so our future consultants (especially in these islands where conditions are favourable) to watch for the signs of placenta prævia *before* bleeding begins. Selective placentography can play an important part here too.

If there is doubt about this Professor Macafee himself has surely dispelled it in his account of discovering *by accident* a number of cases (six, I think) of major placenta prævia at cæsarean section for other reasons.

This too stresses the importance of noting the difference between a high or elevated head not approaching the brim, and merely the unengaged one that does. The advantages that soft-tissue placentography can offer to the discerning outpatient clinician in such cases seem too obvious to mention.

(3) The X-ray risk with ordinary care has been greatly exaggerated according to the most recent reports by enlightened authorities; so too have the number of films needed for placentography. The four mentioned by Professor Macafee have seldom if ever been used by us—one is the more usual.

The London Hospital, London, E.1.

ROBERT PERCIVAL
STANLEY MURRAY.

EFFECT OF HEPARIN AND Ro1-8307 ON KALURESIS

SIR,—In their letter of March 5, Dr. Muldowney and Dr. Banks drew attention to a kaluretic effect after intravascular injections of heparin in short-term experiments in normal and adrenalectomised dogs.

We are able to give comparable results in humans as some of our patients received a diet for the study of diurnal excretory rhythm, described in our article of Feb. 6 as the diet *a* (eight identical meals each day, urine collections every three hours). The patients received heparin (75 mg.) or the heparinoid Ro1-8307 (100 mg.) by intravenous route every six hours.

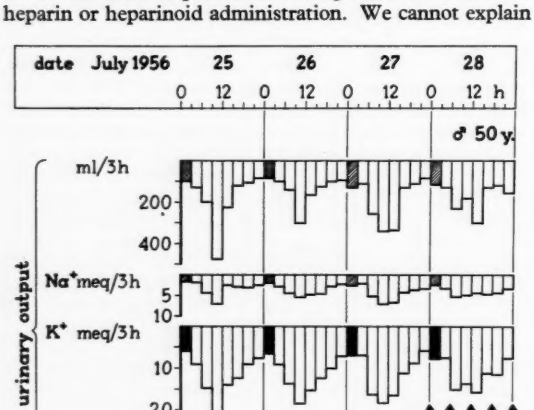
The accompanying figure shows the diurnal excretion pattern of water, sodium, potassium, and creatinine in a patient with coronary insufficiency without signs of heart-failure. The first heparin injection was given on July 28 at 0·00 A.M. When we compare the excretion of potassium in the period 0·00 up till 3.00 A.M. (black columns) on July 25, 26, and 27 with July 28, no increased urinary excretion of this ion was recorded during the three hours after the first heparin dose.

The effect of heparin or Ro1-8307 on urinary sodium and potassium excretion during the three hours after the first intravenous dose in 14 patients is shown in the table. All patients were on the same type of rigorously standardised diet. Mean potassium outputs during identical three-hour period(s) of preceding day(s) are given as control values.

Patient 12 had undergone total adrenalectomy for metastatic cancer of the breast and received as substitution therapy 12·5 mg. of cortisone acetate, 0·25 mg. of 9-α-fluorohydrocortisone, and 2·5 g. of succus liquiritiæ every six hours.

Patient 14 had suffered from Addison's disease of unknown origin and received every six hours 0·1 mg. 9-α-fluorohydrocortisone and 2 mg. of prednisone.

It is apparent that we never found a significant change in the excretion of potassium during the first hours after heparin or heparinoid administration. We cannot explain



Diurnal excretion pattern of water, sodium, potassium, and creatinine in patient 1. No increase of potassium excretion in the three-hour period after the first heparin injection.

COMPARISON OF URINARY EXCRETION OF WATER, SODIUM, POTASSIUM, AND CREATININE IN THE THREE-HOUR PERIOD AFTER THE FIRST INTRAVENOUS INJECTION OF HEPARIN OR Ro1-8307, WITH EXCRETION IN IDENTICAL PERIOD(S) OF THE PRECEDING DAY(S)

Patient no.	Sex	Age	—	Urine vol. (ml. per 3 hr.)	Urine Na+ (mEq. per 3 hr.)	Urine K+ (mEq. per 3 hr.)	Urine creatinine (mg. per 3 hr.)
1	M	50	Control (3 days) ..	105	2·1	6·6	205
			After i.v. heparin..	115	2·5	7·8	210
2	M	46	Control (2 days) ..	135	5·4	18·9	215
			After i.v. heparin..	120	2·3	19·5	195
3	F	50	Control (2 days) ..	300	6·4	18·2	215
			After i.v. heparin..	220	2·0	13·7	180
4	F	61	Control (3 days) ..	130	1·4	7·7	70
			After i.v. heparin..	145	1·6	8·3	70
5	M	52	Control (1 day) ..	185	9·1	10·7	130
			After i.v. heparin..	170	6·3	10·4	145
6	M	58	Control (2 days) ..	75	1·1	8·8	200
			After i.v. heparin..	90	1·9	11·5	205
7	M	17	Control (3 days) ..	220	6·0	8·5	205
			After i.v. heparin..	355	19·8	8·5	210
8	M	56	Control (2 days) ..	105	1·5	17·0	150
			After i.v. heparin..	100	0·9	15·6	160
9	F	17	Control (2 days) ..	260	6·8	17·8	135
			After i.v. heparin..	290	2·6	16·8	130
10	F	17	Control (2 days) ..	260	5·6	13·8	140
			After i.v. heparin..	235	3·6	11·2	130
11	F	31	Control (3 days) ..	95	0·1	3·0	85
			After i.v. heparin..	95	0·1	3·6	85
12	F	40	Control (2 days) ..	115	0·8	14·0	140
			After i.v. heparin..	135	0·8	13·0	150
13	M	46	Control (2 days) ..	195	6·5	26·1	225
			After i.v. Ro1-8307	210	3·6	34·8	235
14	F	36	Control (2 days) ..	275	7·5	11·1	90
			After i.v. Ro1-8307	310	3·5	12·3	105

the interesting but deviating results found in dogs by Muldowney and Banks. They do not mention the weight of their experimental animals, but we have good reason to believe that the dose of heparin they used in dogs was larger than the dose we gave to our patients, when compared on a weight basis. We agree with Muldowney and Banks that the rapid kaluretic effect they found after heparin injections in dogs cannot be ascribed to an alteration in aldosterone secretion and thus must be clearly distinguished from the aldosterone-dependent natriuretic effect we have studied in humans.

Department of Internal Medicine, St. Radboud Hospital, University of Nijmegen, Netherlands.

R. J. A. F. M. SCHLATMANN
H. PRENEN
A. P. JANSEN
C. L. H. MAJOOR.

HÆMOGLOBIN STANDARD

SIR,—In 1955 the Protein Commission of the International Union of Pure and Applied Chemistry considered the problem of standardising the value of the iron content of hæmoglobin in blood, and following their recommendation 100% Haldane became equivalent to an iron content of 14·6 g. per 100 ml.

As a peripatetic pathologist I have had the opportunity to observe that in some laboratories this recommendation has borne no fruit and that the 100% standard remains at 14·8 g. per 100 ml. This may also apply to many laboratories which I have not visited. Upon asking the reason for this non-conformity I have been told that the correction of so small a difference entails the expenditure of a relatively large amount of trouble, and as a peripatetic pathologist does not choose to appear offensively critical of his colleagues, I have accepted so common-sense an answer, for it is true that the difference is a very small one, and clinically insignificant. The real danger, however, is not to the patient but to the pathologist, for in this competitive age the pathologist cannot afford knowingly to expose himself either to the charge of individualism, or of non-conformity, or even (if it must be said) of being behind the times.

Hertford County Hospital, Hertford.

F. C. STALLYBRASS.

N.H.S. DISCIPLINARY TRIBUNALS

SIR,—It is time that a protest was made against the iniquitous system of trying complaints against general practitioners. The harassed general practitioner is at the mercy of any Tom, Dick, or Harry whose dislike he may be unfortunate enough to incur. The decision to proceed with a complaint is in the hands of a lay chairman, who is, therefore, deciding on matters of medical diagnosis and treatment. Even when the whole Service Committee is consulted, there is still a majority of lay persons, and the chairman holds the casting vote. This is as ludicrous a situation as would pertain if a doctor were placed in command of a tribunal hearing complaints against lawyers.

There is, or should be, one system of justice for everybody in this country. The public has full access to the legal machinery, and there is the added safeguard of the General Medical Council. If a doctor is accused of failing in his medical care of his patients, then he should be entitled to the same legal privileges enjoyed by the remainder of the population. Instead, he is subjected to a humiliating and time-wasting procedure in which the scales are weighted heavily against him from the start.

It is my intention, if ever called before one of these tribunals, to refuse to have any communication with the committee whatsoever. It is perfectly legitimate to do this under the N.H.S. Act. In the event of the committee finding against me, then I shall, on appeal to the Minister, provide full information on my side of the case. In the majority of instances these complaints are frivolous. If this procedure was adopted by everyone, the Minister would be in the position of having to reverse many of the decisions of the committee. In this way the proceedings of the committee would fall into disrepute, and something might be done about this unjust and unBritish procedure.

Twickenham. DAVID WHEATLEY.

URINARY EXCRETION OF 5-HYDROXYINDOLEACETIC ACID AFTER REMOVAL OF THE LARGE INTESTINE IN MAN

SIR,—One of us described [1] the effects of removal of the large intestine on the biosynthesis and metabolism of 5-hydroxytryptamine (5-H.T.) in the organism of the rat. Particular attention was paid to the quantitative estimation of the urinary 5-H.I.A.A. as a reliable index of turnover-rate of extracerebral 5-H.T.

A striking reduction (up to 40 or 50%) in the daily urinary excretion of 5-H.I.A.A. was found after removal of the rat's large intestine.

The presence and distribution of the enterochromaffin-cell system and consequently the quantity of 5-H.T. in different parts of the gastrointestinal tract have been extensively studied in many species, although they are practically unknown in man. From the data given by Erspamer [2] it seems, however, that the large intestine contains, even in man, a remarkable amount of 5-H.T. We therefore investigated the rate of 5-H.T. metabolism in seven patients suffering from ulcerative colitis, and operated on for removal of the large intestine. Information on their 5-H.T. metabolism was obtained by estimation of urinary excretion of 5-H.I.A.A. Urine was collected over a 24-hour period and its 5-H.I.A.A. content was estimated by the colorimetric method of MacFarlane et al.[3] In most of the cases urine was collected approximately 6 months after the operation. Healthy subjects, under the same conditions as regards age, diet, and season, acted as controls. Results were as follows:

5-H.I.A.A. content of urine	
Controls (mg. per 24 hr.)	*Operated subjects (mg. per 24 hr.)*
4·24	2·10
4·80	1·65
3·36	0·84
2·70	1·20
1·80	1·15
1·20	1·33
5·87	1·82
1·60	
1·80	
* 3·04±1·24	* 1·44±0·39

$P < 0.05$

* Values expressed as means, plus or minus fiducial limits t=0·05.

These results agree with those obtained by Haverback,[4] who found the daily excretion of 5-H.I.A.A. varying between 0·36 and 1·06 mg. in a patient whose large and small intestine had been resected. They suggest that in man too gastrointestinal mucosa is the main site of production of 5-H.T. appearing in the blood, and hence of urinary 5-H.I.A.A.

Institute of Pharmacology, University of Parma, Parma, Italy. G. BERTACCINI.

Surgical Clinic, University of Bologna, Bologna, Italy. S. CHIEPPA.

1. Bertaccini, G. *Naturwiss.* 1958, **45**, 548.
2. Erspamer, V. *Rendiconti scient. Farmitalia*, 1954, **1**, 1.
3. MacFarlane, P. S., Dalgliesh, C. E., Dutton, R. W., Lennox, B., Nyhus, L. M., Smith, A. N. *Scot. med. J.* 1956, **1**, 148.

AGRANULOCYTOSIS AND THROMBOCYTOPENIA ASSOCIATED WITH ARTHRIPAX

SIR,—In the case described below, pancytopenia developed after the patient had been taking a preparation containing salicylamide, mephenesin, and aluminium glycinate for 6 weeks.

A man of 49 was first seen on April 7, 1959. He was obviously very ill; his temperature was 104°, and he was complaining of a sore throat, which was found to be very inflamed, with three or four small pustules on each side. He had been taking 2 'Arthripax' tablets three times a day for the previous 6 weeks. Each tablet contains salicylamide (gr. 5), mephenesin (gr. 1), and aluminium glycinate (gr. $1^1/_2$). The tablets had been given to him by a "man who did massage" (not a registered physiotherapist). His first symptom, a sore throat, developed on the afternoon of April 5.

Blood examination, carried out within 48 hours of first symptoms, and within 2 hours of first being seen, showed hæmoglobin 11·8 g. per 100 ml.; the white cell count (W.B.C.) was 20 (Dacie's method [5]: normal 4000–10,000). As there were so few white blood-cells, no differential count was done. The blood-urea was 40 mg. per 100 ml. A diagnosis of agranulocytosis was made; and a pint of stored blood was given. A swab taken from the throat yielded a growth of pyogenic streptococci, sensitive to penicillin and streptomycin, and he was given these drugs.

April 9: no white cells (Dacie's method); none in 100 oil-immersion fields (normally 2–4 are found per oil-immersion field).

April 10: a pint of fresh blood was transfused vein-to-vein. Towards the end of the transfusion, the patient had a severe rigor, and was given an injection of 25 mg. of promezathine.

April 11: the patient deteriorated; he was tired, weak, and unable to sleep, his throat was covered with a white purulent exudate, the lymph-nodes were enlarged and tender, and he was jaundiced. W.B.C. 28; no polymorphs in the stained film. Platelets reduced to 23,000 per c.mm. (normal 250,000–400,000). Serum-bilirubin 5·8 mg. per 100 ml. (normal 0·5–1·0).

April 12: he was much worse and seemed to be dying. He was given intravenous tetracycline and prednisone. Hæmoglobin 9·7 g. per 100 ml., W.B.C. 750 per c.mm.; in 50 oil-immersion fields there were 7 lymphocytes and 1 monocyte, no polymorphs.

April 13: W.B.C. 1500, no polymorphs. He appeared a little better.

April 14: W.B.C. 1300, only 1 polymorph in 50 oil-immersion fields. Clinically, there was a slight improvement.

April 15: W.B.C. 2100 (100 polymorphs, with an occasional myelocyte).

April 17: the patient was improving, W.B.C. 5900 (nearly 4000 polymorphs).

4. Haverback, B. J., Davidson, J. D. *Gastroenterology*, 1958, **35**, 560.
5. Dacie, J. V. Practical Hæmatology. London, 1956.

April 18: jaundice fading, serum-bilirubin 1·4 mg., alkaline-phosphatase 7 King-Armstrong units (within normal limits), thymol turbidity 5 units (normal 1–4), zinc sulphate 20 units (normal 1–12), and ammonium sulphate 6·5 units (normal 1–6).

April 19: W.B.C. 9600 (about 7000 polymorphs).

He made a complete recovery and was discharged on May 5 and has remained fit.

In addition to blood-transfusion the patient was treated with penicillin, streptomycin, and intravenous tetracycline, nystatin, and prednisone.

It is assumed that arthripax was the cause of the illness. Whitby and Britton [6] list over 40 preparations that have been thought to cause agranulocytosis, and Wintrobe [7] mentions others, but arthripax is not included. Platt [8] described a case of thrombocytopenia following arthripax; and Hillier [9] recorded another. In both these cases, although the platelets were worst hit, the other blood elements suffered.

Jaundice can occur in agranulocytosis [7]; in our patient we do not think the jaundice was due to mismatched blood or to red-cell destruction, but probably to liver dysfunction—a view supported by the altered flocculation tests.

It is hard to explain the absence of hæmorrhages, despite the dangerous level of the platelets.

The patient seemed to respond better to intravenous tetracycline than he did to penicillin and streptomycin.

The value of blood-transfusion in these cases is not proven. Whitby and Britton [6] feel transfusion is of doubtful value; Wintrobe [7] regards the results as inconclusive; and Cecil [10] does not mention transfusion in the treatment of this condition. We know of no evidence that fresh blood contains a factor that can stimulate the marrow, and it seems unlikely that the number of transfused polymorphs would be of any value.

Agranulocytosis caused by drugs (except amidopyrene) usually appears during or after the 4th week of continuous treatment, but the onset may be earlier in sensitised patients. It is probably useless to do routine weekly white counts when the patient is on a potentially dangerous drug, as the onset of agranulocytosis is sudden—within a matter of a few hours.[10] All that can be done is to warn the patient who is taking a potentially dangerous drug that if fever or a sore throat develops he should stop the drug and seek immediate advice.

We wish to thank Dr. J. G. Green for his courtesy in letting us use the notes of a patient under his care.

R. AIDIN
P. MURPHY.

Worthing.

VITAMIN E FOR ATHLETES

SIR,—Three years ago I learned from some of our athletes returning from the Melbourne Olympic Games that vitamin E was being given extensively to athletes in Australia, and the phenomenal success of their athletes and swimmers encouraged me to carry out a trial here. We had then no detailed information; so our first trial was very much a pioneer effort, for which we chose members of the athletic club over a period of some two months. Although the results were statistically of little value we were sufficiently impressed by some of the clinical results to attempt a further trial last year.

Our impression was that its value, if any, lay in increased stamina and delayed fatigue; so this year members of our senior eight rowing team volunteered for the trial, which was carried out over a period of three months. Again the results were very encouraging, especially from the clinical point of view, the crew having the most successful year in the annals of the club.

This year we are attempting a much more comprehensive trial using as our volunteers six trained athletes, six untrained but starting training, and six untrained who will remain so, having no interest whatever in games or exercise of any kind. The trial has been planned statistically using several physiological tests at regular intervals under exactly similar conditions each time and including forced expiratory volume and a modified Cotton ergometer. The trial will be carried out over a period of three months and is hoped will provide a true index of the value of vitamin E in athletics.

Student Health Department,
Queen's University of Belfast. WILSON JOHNSTON.

A PORTABLE FREE-FIELD AUDIOMETER

SIR,—The audiometer described by Mr. Denes and Mr. Reed [1] would no doubt be very useful to obtain some approximate indication of the hearing capabilities of a subject who could not be tested using a normal audiometer.

Pure-tone audiometry is normally carried out by earphone listening and if the equipment complies with all the requirements of British Standard 2980, should enable readings from the same subject to be repeated to an accuracy of 5 dB. The use of earphones enables each ear to be assessed separately and in particular it makes the measurement independent of the sound-reflecting quality of the room in which the test is carried out.

When a loudspeaker reproduces a fixed frequency of pure tone in an ordinary room, multiple reflections of sound occur from the walls and ceiling. At one point in the room the reflected sounds can reinforce each other to give a point of high sound intensity, while at another point in the room, only a short distance away the reflected sounds tend to cancel out to give a point of minimum sound intensity. This can easily be observed using an ordinary radio or television receiver to reproduce the 1000 c/s "tuning note" which the B.B.C. broadcast prior to the commencement of the programme. If the observer blocks one ear, the sound heard by the other ear will be found to vary considerably in intensity when the head is moved just a few inches in one direction or the other. It may even be found that the sound heard in a corner of the room opposite the loudspeaker is louder than when the ear is only 3 or 4 feet away from the loudspeaker. This simple experiment will illustrate the powerful effect of room reflections on the sound reaching the eardrum.

To obtain acoustical conditions free of these disturbing reflections an acoustically treated "anechoic" room is necessary and this can be very costly. The *Wireless World* article makes reference to the subjective calibration of the invention in such an "anechoic" room and this calibration does not correspond to the conditions under which it will normally be used.

Wembley,
Middlesex. J. P. ASHTON
Director and Chief Engineer, Amplivox Ltd.

*** Mr. Ashton's letter was shown to Mr. Denes and Mr. Reed and their reply follows.—ED. L.

SIR,—Concerning Mr. Ashton's comments on the use of the free-field portable audiometer, we have no doubt that his observations with reference to acoustics and room conditions are quite accurate, yet in relation to the use of this instrument as described in *The Lancet*, they seem irrelevant.

Mr. Ashton writes, as if this is a minor point, "the audiometer would no doubt be very useful to obtain some approximate indication of the hearing capabilities of a subject who could not be tested using normal audiometry." In fact, this is almost the only reason for this instrument. One other use is to prepare a child for normal pure-tone audiometry.

In our article, apart from the description of the instrument's physical properties, all else was devoted to its use in circumstances in which normal pure-tone audiometry could not be carried out.

The procedure will show whether at some time or other the child will respond in some way or other to various frequencies.

6. Whitby, L. E. H., Britton, C. J. C. Disorders of the Blood. London, 1957.
7. Wintrobe, M. M. Clinical Hæmatology. London, 1951.
8. Platt, R. *Brit. med. J.* 1958, ii, 1577.
9. Hillier, F. F. *ibid.* 1959, i, 170.
10. Cecil, R. L. Textbook of Medicine, 1955.

1. Denes, P., Reed, M. *Lancet*, 1959, ii, 830 (a technical description of the equipment appeared in *Wireless World*, Dec., 1959).

If the child does respond, then this is a positive indication of some hearing at that frequency. In the fullness of time a qualitative picture can be built up which, together with other evidence, will enable the clinician to establish a reasonable diagnosis.

There are many children who, in these days of emphasis on early and correct diagnosis, present a behaviour pattern which makes it difficult to establish whether the child is mentally retarded, psychotic, or deaf. Often, of course, a slight degree of many of these conditions is present.

Awareness of a rattle may give insufficient information. Awareness of pure tones may give much more information. The exact level is not always so important in such circumstances, and often cannot be obtained from a particular child for too long a lapse of time. However a qualitative picture as may be given by the use of this instrument will often enable the clinician more readily to make a decision on further training.

Phonetic Department, University College London, London, W.C.1. P. DENES.

Audiology Unit, Royal National Throat, Nose and Ear Hospital, London, W.C.1. MICHAEL REED.

JUDO

SIR,—We were interested to see reference [1] to judo as a possible alternative to boxing in schools. As holders of both medical qualifications and judo black belts, we write to support the suggestion that the health and educational value of judo deserves serious attention.

The immediate practical value of judo as a means of self-defence is, we feel, only a minor consideration. Real proficiency requires intensive work along lines different from those of judo as a sport, although the latter can form an ideal basic training for the subsequent study of self-defence.

If fact the most direct application of judo skill to ordinary life comes from the training and constant habituation in falling safely from all angles. For example, motor-cycling judo players sometimes have striking demonstrations of the value of a spontaneous judo fall. The management of the body in falling is the beginning of judo training, and its achievement may have more than superficial effects; it appears to play a part in the increasing self-confidence often shown by nervous young men who have taken up judo.

But no sport can be assessed on its specific applications: much more important is the influence on personal development as a whole and its enjoyment value. These things are not entirely to be dissociated, for, while development depends on effort, effort to be constructive must also be enjoyed.

Here judo does seem to be of wider value than boxing by virtue of its greater scope and adaptability. Judo attack and defence comprise many different types of movement, and the style of each individual, and the actions which he principally uses in attack, tend to select themselves according to his physique and natural inclinations. Each can make the most of his own size, build, and proportions (there is no need to match opponents for weight and size). Progress in judo is marked by a system of grading according to skill, and it is this that provides the basis for matching opponents. The big man and the small man of equivalent skill fight, as it were, with different weapons but can be equally effective. Contests between them will thus be decided mainly by such factors as confidence, personality, and style. Often aggressiveness of movement rather than size or power determines the result.

A judo contest can be a very intense process, but the demands of judo training arise in a gradually progressive manner which can allow even a very weak novice to adapt himself to them smoothly without the deterrent effect of trauma, mental or physical, at a stage before he is ripe to withstand it. He can get something very positive out of the early stages even if he never acquires much contest proficiency, although the latter is one of the aims upon which his training is oriented and which gives it meaning and direction.

The basic elements common to all varieties of judo style and action are principles of posture and movement which could be discussed at great length, but in a well-guided training they are of course assimilated in practice rather than presented intellectually. In essence the postural demands of judo proficiency are the release of the natural flow and coordination of movement from the influences which so commonly distort them. Any sport at its best should have a similar effect, but judo seems to differ from others in that correct natural movement is so critically and specifically essential to effectiveness.

Furthermore, in judo this posture needs to be a continuous background to all activity, whereas, for example, a golfer (in whose actual stroke, posture is equally important) experiences this in a much more specialised connection and is under no demand to maintain it between one stroke and the next. Hence the lessons learnt on the judo mat seem to permeate general activity more potently than those learnt in other sports.

We think that this is one of the major benefits of judo in physical development. This is not to say that judo practice is not also accompanied by improvement in emotional as well as physical poise and often too by an impressive gain in weight and generalised muscular development. Of course, judo practice needs to be effectively supervised and wisely guided by a sound teacher and these are still scarce (but getting less so). Thus the major obstacles to the development of judo in schools are this difficulty in finding good instructors, and occasional prejudice against judo, based on misconceptions as to its true nature.

London, S.W.10. H. M. HODKINSON.
Oxford. R. M. MORRIS-OWEN.
Wroughton, Wiltshire. H. M. WILLIAMS.

1. *Lancet*, Jan. 23, 1960, p. 210.

Parliament

Children in Prison

ON April 6 under the ten-minute rule Mr. ALAN BROWN asked for leave to bring in a Bill to restrict the committal to prison of children under 16 years of age and to provide for the transfer to remand homes or remand centres of children who have been so committed. Everyone had been shocked when it came to light three weeks ago that a 14-year-old girl, originally in trouble for playing truant from school, had been sent to Holloway on remand and placed in a ward with women accused of murder. On March 22 Mr. Brown had visited Wormwood Scrubs, and found nine boys below school-leaving age imprisoned there. There were two prison blocks within the outer wall of this prison. One block was the " boys' " prison and the other was the " men's " prison. The boys' prison contained persons in the age-range 14–21, and there was a real danger of the possible criminal indoctrination of the schoolboys by the older youths of the " young adult " class. The children were locked individually in the ordinary type of bare comfortless prison cell measuring about 7 ft. by 10 ft. There were no educational facilities.

The concept that a child might not be imprisoned for any reason whatsoever before he or she reached the normal end of compulsory school attendance was already the accepted practice in most countries. The argument which had received most publicity against it in this country was that if we released the children from prison there was nowhere else to send them. But if shortage of remand homes was to be pleaded, why, he asked, had so many been closed down in recent years? Between 1951 and 1955 18 remand homes owned by local authorities were closed down, with a consequential loss of 495 places, and the country was left with 36 remand homes for boys, 14 remand homes for girls, and 1 remand home for boys and girls all provided by local authorities, and 10 remand homes owned by voluntary organisations. Since then there had been a net loss of 8 further remand homes. So far as he could ascertain 120 to 150 children were at the moment lying in prison.

QUESTION TIME

Antibiotics in Animal Feeding-stuffs

Lord DOUGLAS OF BARLOCH asked H.M. Government what was the extent of the use of antibiotics in the feeding of animals intended for human consumption.—Earl WALDEGRAVE, the joint parliamentary secretary of the Ministry of Agriculture, Fisheries, and Food, replied: The sale or supply of compound feeding-stuffs and supplements containing antibiotics, other than on veterinary prescription, is confined by statute to pig and poultry foods containing penicillin, aureomycin, or oxytetracycline in certain prescribed and limited proportions. Under regulations, based on advice from the Agricultural Research Council in consultation with the Medical Research Council, the inclusion of these substances in manufactured feeding-stuffs is restricted to food for young pigs and poultry intended for early slaughter. Within the permitted categories of pigs and poultry the feeding of antibiotics, which may lead to improved rates of growth and better food conversion, is thought to be fairly widespread, but I regret that no precise information is available. This subject, however, is complex, and a joint committee of the Agricultural Research Council and the Medical Research Council is shortly to review the whole problem. Lord DOUGLAS OF BARLOCH: May I ask whether there is any means by which a person purchasing either poultry or pig products can know whether they have been treated in this way or not? Earl WALDEGRAVE: No, I do not think there is any means.

Hospital Building

Hospital capital expenditure for 1938–39 was of the order of £32 million, or about 0·17% of the national income at the time. The most nearly comparable figure for 1954–58 is of the order of £57 million, which would correspond to about £16 million at the prices ruling in 1935–39. It is about 0·09% of the present national income.

Merit Awards

For 1959, 216 awards were given to consultants, divided by specialties as follows:

General medicine	42	General surgery	36
Diseases of the chest	7	Anæsthetics	16
Mental health	13	Neurosurgery	10
Neurology	2	Plastic surgery	4
Pædiatrics	8	Thoracic surgery	4
Radiology	5	Orthopædic surgery	11
Radiotherapy	1	Dentistry	8
Pathology	16	Ear, nose, and throat	3
Dermatology	5	Obstetrics and gynæcology	21
Ophthalmology	4		

Public Health

Infectious Diseases in England and Wales

Disease	Week ended March 5	12	19	26*
Diphtheria	2	3	. . .	1
Dysentery	1706	1844	1874	2067
Encephalitis:				
Infective	. .	2	4	. .
Postinfectious	2	2	2	. .
Food-poisoning	268	193	174	217
Measles, excluding rubella	2355	2141	2250	2198
Meningococcal infection	18	25	23	21
Ophthalmia neonatorum	25	29	31	26
Paratyphoid fever	2	10	1	2
Pneumonia, primary or influenzal	596	501	418	418
Poliomyelitis:				
Paralytic	6	6	4	2
Non-paralytic	3	3	4	2
Puerperal pyrexia	210	203	166	178
Scarlet fever	1142	1077	1176	1152
Smallpox	. .	. .	. .	. .
Tuberculosis:				
Respiratory	447	455	469	419
Meninges and C.N.S.	6	9	10	4
Other	55	61	59	46
Typhoid fever	1	1	1	1
Whooping-cough	798	782	896	903

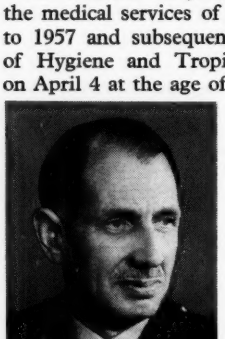
* Not including late returns.

Obituary

JAMES MacCONNELL KILPATRICK

K.B.E., C.B., M.B., LL.D. Belf., D.P.H.

Air Marshal Sir James Kilpatrick, director-general of the medical services of the Royal Air Force from 1951 to 1957 and subsequently dean of the London School of Hygiene and Tropical Medicine, died in London on April 4 at the age of 58.



Elliot & Fry

An Ulsterman born and bred, he was educated in Belfast, graduating M.B. from Queen's University in 1924. The following year he joined the Royal Air Force. Even as a junior officer he was outstanding and it was obvious that he would be a candidate for the highest rank in the medical branch. He had a leaning towards pathology and tropical medicine, and in 1927 he was selected for specialist training. He was employed on clinical and pathological duties at Halton from 1927 to 1931, including the investigation and control of an epidemic of cerebrospinal fever at Uxbridge in 1931. For his important contributions to preventive medicine he was awarded, in 1932, the Arnott gold medal of the Irish Medical Schools and Graduates Association. From 1931 to 1933 he was pathologist to the R.A.F. in Iraq, but on his return to this country he switched over to physiology as applied to aviation medicine for two years before taking further appointments as pathologist at R.A.F. hospitals in England.

Early in 1939 he joined the medical directorate staff at the Air Ministry as a member of the hygiene department, and on the formation of the Flying Personnel Research Committee he was appointed secretary. On the outbreak of war he became assistant director of hygiene, and for three years contributed much to the development of sound hygiene and sanitary practices at all R.A.F. units at home and abroad. During 1943 and 1944 he was the R.A.F. principal medical officer in West Africa, and he was so successful in reducing the incidence of disease among personnel there that the occupied hospital bed-state was reduced ten-fold. He was the first R.A.F. medical officer to do the full Staff College course, and he graduated from it in 1946, with the highest marks.

After the war, he was appointed director of hygiene and research at the Air Ministry, and he also served as chief executive officer of the Flying Personnel Research Committee until 1950, when he was promoted to deputy director-general of medical services. In 1951 he became director-general. His term of office came at a difficult period, for the R.A.F. was being reorganised to streamline it to meet the changed concept of its functions, and, as the result of the Waverley Committee's recommendations, much had to be done to improve the career and emoluments of the medical officers, but Kilpatrick carried out the necessary changes efficiently and expeditiously.

H. E. W. writes:

" James Kilpatrick was a most likeable man with considerable charm and courtesy. He was quiet and unassuming, a characteristic which he maintained throughout his career, treating the most junior with every consideration. Though a patient listener, he spoke his mind frankly and was firm in his decisions and actions. He never deviated from what he considered to be

his duty. He was able, accurate, and shrewd both as a doctor and an administrator. A deep thinker with a wide and practical knowledge of many subjects, he was a tower of strength on committees, expressing his views so clearly, concisely, and logically that he seldom failed to gain his point. He had the confidence of all those who ever worked with him."

When he retired from the R.A.F. in 1957 he became dean of the London School of Hygiene and Tropical Medicine, and D. D. R. writes:

"The transition from a Service hierarchy to the position of *primus inter pares* in an academic institution must have been difficult, but Sir James soon allayed any anxieties that might have arisen on this score. He was no martinet. Indeed, his administration of the school's affairs was distinguished by his gentle exercise of authority and his steadfast maintenance of both the dignity of his office and the warmth of his personal relationship with his colleagues. With anyone who sought his advice or help he generously shared his wisdom, experience, and his time. Students, coming as strangers to this country, must have been especially grateful for his kindly welcome.

"In 1958 he was elected president of the section of epidemiology and preventive medicine of the Royal Society of Medicine, and he brought to the conduct of the section's business the modesty, sincerity, and integrity which shone through all his actions, and the width of his outlook was reflected in his presidential address on the growth of the Royal Air Force medical branch as an organisation for prevention medicine.

"He drove no-one hard except himself. By his devotion to his duty he may well have cut short his term of office at the school. But in that span of time no man could have inspired more affection and respect than he did."

Sir James married in 1928 Marjorie, daughter of Charles Drean of Belfast, who survives him with two sons. One is in the medical branch of the R.A.F. and the other a medical student.

The honours bestowed on him included appointment as honorary physician to the King in 1951, C.B. in 1952, K.B.E. in 1953, and the honorary LL.D. of his alma mater in 1957.

JOSEPH JEFFERSON COULTHARD

M.B. Edin., F.R.C.S.E.

Dr. Joseph Jefferson Coulthard, who died on March 29 at the age of 62, retired last year after practising in Edenbridge for 25 years.

He qualified from the University of Edinburgh in 1922 and took the F.R.C.S.E. in 1930. For many years he was surgeon to the Edenbridge War Memorial Hospital, and of late years he had acted as anæsthetist. Till 1958 he was chairman of the medical committee of the hospital. His friends and patients gave him a presentation at the end of the late war; and on his retirement they gave him a scroll and a cheque, and a bronze plaque was placed in the hall of Edenbridge Hospital in recognition of the work he did there as well as for the town.

P. H. M.-B. writes: "Dr. Coulthard was a good sportsman and a fine shot and he fitted in well with the countryside he loved so well, so that he was known and esteemed beyond the borders of his own practice. As he was a good judge of horses and dogs, he became a particular supporter of the Edenbridge annual show of which he was president in 1950, and thereafter he was patron as well as honorary medical officer. He was also one of the founders and supporters of the particularly virile Edenbridge Medical Society. His personal popularity, enriched by kindly witticisms, was immense and his visits to his more humble patients were often rendered more than ever welcome by the gift of a cock pheasant, or a brace of partridges. He was much loved in the district and was always regarded as a special friend by rich and poor alike."

News

University of Oxford

Lord Adrian will give the Romanes lecture on May 24, at 5 P.M., in the Sheldonian Theatre. He will speak on factors in mental evolution.

The George Herbert Hunt travelling scholarship for 1960 has been awarded to R. D. Stedeford.

University of London

Dr. C. F. Harris has been re-elected vice-chancellor of the university for 1960–61.

Dr. K. W. Cross, reader in physiology at St. Mary's Hospital Medical School, has been appointed to the chair of physiology at the London Hospital Medical College.

Dr. Cross qualified from St. Mary's Hospital in 1940. After holding house-appointments at Hillingdon Hospital and St. Mary's, he became deputy medical superintendent at Amersham E.M.S. Hospital. He spent a year with the Friends' Ambulance Unit in China before he became lecturer in human physiology at St. Mary's Hospital Medical School in 1947. He was appointed to the readership in the department in 1953. His published work includes papers on the respiration of the newborn.

University of Durham

On July 1 the honorary degree of D.SC. is to be conferred on Dr. Donald Hunter.

A postgraduate course on industrial health is to be held at the Medical School, King's College, Newcastle upon Tyne, 1, on Thursdays, from April 28 to June 16, at 2.30 P.M. The speakers will include Lord Taylor, Dr. R. I. McCallum, Dr. G. L. Leathart, Prof. R. C. Browne, Mr. D. N. Walder, Mr. P. N. Robson, Dr. H. G. Miller, Prof. J. T. Ingram, Dr. J. M. L. Howat, and Dr. Sibyl Horner. Further particulars may be had from the assistant registrar at the Medical School.

University of Birmingham

The honorary degree of D.SC. is to be conferred on Sir Geoffrey Jefferson.

Mr. F. C. Walker has been appointed lecturer in surgery.

University of Dublin

The following have been awarded the diploma in obstetrics:
S. Ahmed, S. H. M. Logan, M. L. O'Flaherty, T. F. Shaw.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting on April 4 with Mr. Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship:

A. C. Arntzenius, C. Chin Hin Chew, Devappa Gowda Chinniah, J. L. C. Dall, M. G. Dunnigan, Ahmed Badr Eldin Sayed Ibrahim, J. L. J. Ives, Julia A. Keane, A. L. Linton, Shoukat Madmud Malik, Bhattarahalli Gururao Srinavasa Murthy, Iqbal Hussain Randhawa, Allan Sinclair, W. D. Smith, R. G. Spector (qua physician); W. M. Borthwick, R. J. Scothorne (qua surgeon).

Hunterian Society

The subject for the 1960 essay competition for the gold medal of this society is the management of chronic arthritis in general practice. The competition is open to all general practitioners resident within the Commonwealth. Further details may be had from the hon. secretary, Mr. George Qvist, 72, Harley Street, London, W.1.

South West Metropolitan Regional Hospital Board

The following have been awarded prizes in the board's 1959 competition:

Consultants and S.H.M.O.s.—Mr. Dermot Pierse and Dr. H. O'Donoghue (joint entry), Dr. D. Kendall.

Senior registrars, registrars, and J.H.M.O.s.—Dr. A. Poteliakhoff, Dr. P. Sewell.

Senior house-officers and house-officers.—Dr. J. D. Maynard, Dr. C. P. Broad.

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr. J. L. Livingstone at the institute, in the grounds of the Brompton Hospital, Fulham Road, S.W.3, on Fridays, at 5 P.M. from April 22 to July 8.

Midland Thoracic Society

The following officers and council members have been elected for the 1960–61 session:

President, Dr. G. R. W. N. Luntz: hon. secretary, Dr. H. E. Thomas; council, Dr. A. O. Bech, Dr. B. T. Davis, Dr. A. W. B. Macdonald, Dr. S. Z. Kalinowski.

C. H. Milburn Prize

This prize (£100) for an essay or study on forensic medicine is offered for the first time this year. Any doctor may enter. Further particulars may be had from the secretary of the British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

Feeding of Antibiotics to Farm Animals

The Agricultural and Medical Research Councils have set up a joint committee to examine the possible consequences of the feeding of antibiotics to farm animals and to consider whether this practice constitutes any danger to human or animal health. Lord Netherthorpe is to act as chairman, and Prof. A. A. Miles has agreed to take the chair of a scientific sub-committee which will examine the evidence in detail and place its findings before the main committee.

Current Trends in Cardiology

The Chest and Heart Association will hold a symposium on this subject at 1, Wimpole Street, London, W.1, on Wednesday, June 8, at 3.30 P.M. The speakers will be Dr. K. Shirley Smith, Dr. Maurice Campbell, Dr. G. W. Hayward, Dr. Frances Gardner, Dr. Walter Somerville, and Dr. J. N. Mickerson. Further particulars and tickets (25*s*.) may be had from the association, Tavistock House North, W.C.1.

First British Congress on the History of Medicine and Pharmacy

This congress, organised by the faculty of the history of medicine and pharmacy at the Society of Apothecaries of London, in cooperation with the Royal College of Physicians of London, the Royal College of Surgeons of England, and the Royal Society of Medicine, will be held in London, on Sept. 29 and 30. Further particulars may be had from Dr. F. N. L. Poynter, Wellcome Historical Medical Library, Wellcome Building, Euston Road, N.W.1.

E.E.G. and Clinical Neurophysiology in Pædiatric Problems

The Institute of Child Health is holding a course on this subject on Saturday and Sunday, June 18 and 19, at The Hospital for Sick Children, Great Ormond Street, London, W.1. The speakers will be Dr. Otto Magnus (Wassenaar, Holland), Dr. J. A. V. Bates, Prof. H. L. Teuber (New York), Dr. R. Rudel (New York), Dr. P. B. Bradley, Dr. Giuseppe Pampiglione, and Dr. J. A. Simpson. Further particulars may be had from Dr. G. H. Newns, at the institute.

Leverhulme Trust Fund

The third report of this Trust—which is to be the first of a series of triennial reports—covers 1956 to 1958. During these years the Trust allocated £593,000, of which almost a third was given to medical research.

Grants include: £9100 to the Institute of Laryngology and Otology, London, for research fellowships; £35,000 to the Middlesex Hospital Medical School, London, for scholarships at the Institute of Clinical Research; £10,700 to the Mental Health Research Fund for research fellowships; £9500 to St. Mary's Hospital Medical School, London, for biochemical research; £58,100 to the Royal College of Surgeons of England for research fellowships in dental surgery, anæsthetics, physiology, and for general research; £14,000 to the London School of Hygiene and Tropical Medicine for research in industrial medicine.

British Diabetic Association

A medical and scientific section of this Association has been set up, with Prof. F. G. Young, F.R.S., as chairman and Dr. J. M. Stowers and Dr. D. A. Pyke as hon. secretaries. Inquiries about membership should be sent to the Association, 152, Harley Street, London, W.1.

International Federation of Surgical Colleges

A meeting of the Federation is to be held at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, from Oct. 18 to 20. The theme of the meeting is to be the training of surgeons.

Postgraduate demonstrations in psychiatry and neurology will be given at St. George's Hospital Medical School, London, S.W.1, at 5 P.M. on Thursdays, from April 28 to June 16.

At a meeting of the Medical Society of the Roehampton Plastic Centre on Thursday, April 28, at 8 P.M., at the centre, London, S.W.15, Mr. Guy Pulvertaft will speak on advances in hand surgery.

Copies of the *Digest of Statistics of Incapacity* for 1956–57 can now be had from the statistics division of the Ministry of Pensions and National Insurance, 1, Adam Street, London, W.C.2.

Copies of a new British standard for hospital pressure sterilisers for water (B.S. 3213: 1960) may be obtained (6*s*. each) from the British Standards Institution, Sales Branch, 2, Park Street, London, W.1.

Diary of the Week

APRIL 17 TO 23

Wednesday, 20th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Comparative Medicine.* Prof. R. A. McCance, Dr. G. S. Dawes, Dr. K. W. Cross: Physiology of the Newborn Animal.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. M. T. Morgan: Economics of Local Authority Pest Control.

Thursday, 21st

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4.15 P.M. Dr. B. D. Wyke: Human Cerebral Circulation. (Arnott demonstration.)

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Dr. J. D. Fulton: Experiments on Transformation by DNA. Dr. C. S. Leithead: Influence of Water Intake on Sweating in Hot Climates. Dr. W. E. Ormerod: Cell Inclusion and the Epidemiology of Rhodesian Sleeping Sickness. Prof. A. W. Woodruff, Dr. S. S. Bell: Clinical Trials with New Synthetic Amœbicides.

Friday, 22nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. Kenneth Bloor: Natural History of Arteriosclerosis of the Lower Extremity.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics.* Miss Isabella Forshall: Prognosis for Children Undergoing Operation During the First Few Weeks of Life. (Presidential address.)
8.15 P.M. *Obstetrics and Gynæcology.* Dr. H. Payling Wright, Mr. Harold Dodd, Mr. W. G. Fegan, Mr. Alan Curtis: Treatment of Varicose Veins in Pregnancy.

Appointments

BROCKLEHURST, J. C., M.D. Glasg., F.R.F.P.S.: assistant physician in geriatrics (S.H.M.O.), Bournemouth and East Dorset group of hospitals.

COCKERSOLE, F. J., M.B. Birm., M.R.C.O.G., M.M.S.A.: consultant obstetrician and gynæcologist, West Cumberland group of hospitals.

MCKEITH, MARGARET H., M.B. Durh.: assistant M.O. (maternal and child welfare), Northumberland.

O'REGAN, JOSEPHINE M. M., M.B.: assistant M.O. (maternity and child welfare), Scunthorpe area of Lindsey.

Manchester Regional Hospital Board:

BEARE, M. S., M.B. N.U.I., F.R.C.S.: assistant chest physician, Baguley Hospital, Manchester.

FRASER, J. P., M.B. St. And., F.R.F.P.S.: part-time consultant E.N.T. surgeon, Bury and Rochdale Hospital centres.

WILSON, J. A. C., M.B. Edin., M.R.C.P.: consultant physician, Salford group of hospitals.